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Market and Business Analysis of Microthreads

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Market and Business Analysis of Microthreads

A Major Qualifying Project Report

Submitted to the Faculty

of the

WORCESTER POLYTECHNIC INSTITUTE

in partial fulfillment of the requirements for the

Degree of Bachelor of Science

in Management Engineering, Biomedical Engineering Concentration

by

______________________________
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Date: 29th April 2009

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Professor Helen Vassallo, Major Advisor

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Professor George Pins, Co-Advisor
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Abstract

Cardiovascular disease is the number one cause of death in the United States, with myocardial infarctions adding to the severity of the disease. Infarcted tissue is dead heart tissue that no longer has contractile properties and is very brittle and thin. Professors at Worcester Polytechnic Institute are researching and refining a new technology known as Microthreads that have demonstrated the potential to aid in the regeneration of healthy heart tissue. The purpose of this study was to determine whether this technology is worth pursuing for the cardiac market. Based on the research conducted for this review, Microthread technology will have a promising future in the cardiac market when it is fully developed. However, Microthread technology is still very early in its development and to limit its use to the cardiac field at this time is not considered the optimal direction to pursue in order to develop its full market potential. It may be more judicious at this stage of development for the architects of this technology to license the technology to other researchers, including the area of stem cell research, to increase the potential for this product to gain broad acceptance throughout the medical industry.
Executive Summary

Cardiovascular disease is the number one cause of death in the United States\(^1\). In 2005, 80.7 million people were diagnosed or living with cardiovascular disease, 8.1 million of whom had suffered from a myocardial infarction\(^2\). Of this 8.1 million, 156.8 thousand people died as a result of the infarcted tissue of the heart. With so many people affected by this disease, and thousands more being diagnosed with this disease everyday, the medical establishment is on constant vigil for new and improved medical procedures and products that can help reduce or cure infarcted heart tissue.

Professor George Pins of Worcester Polytechnic Institute has patented a new biomedical product known as Microthreads, which can aid in the repair of infarcted heart tissue. Microthreads are thread-like structures made of the naturally occurring proteins collagen or fibrin, which are biodegradable. The thread-like strands, as thin as a piece of human hair, can be seeded with therapeutic cells or other restorative agents along the exterior surface to create “living” threads. These Microthreads can then be sewn directly into infarcted heart tissue, anchoring the seeded stem cells and/or therapeutic agents in the diseased tissue.

There are several medical devices and procedures currently available (listed below) that aim to duplicate this novel approach of delivering regenerative and therapeutic cells directly to the heart to treat infarcted tissue. Unfortunately, they all fall short because they either do not have the capability of securing the quantity of therapeutic agents to the affected area or they are not capable of supporting the wide range of therapeutic agents that the structural matrix of the Microthread can. These techniques include:
• Injecting cells directly into the heart through the thoracic cavity
• Balloon stents to deliver therapeutic cells embedded in the stent structure
• Intravenously placing therapeutic cells into the blood stream and allowing them to travel to the heart
• A heart patch that requires removing the dead portion of the heart, invasively through surgery, and sewing new, healthy tissue into the gap

Professor Pins has requested this investigation to determine if a strong market potential for this technology exists and what steps should be taken to increase its likelihood of success in the clinical world. This investigation focused heavily on the cardiac market and the business potential for this product in that market. This research paper provides an overview on myocardial infarctions, the prevalence of this disease within the United States, cardiac care stakeholders, and competing technologies to establish a baseline to gauge the viability of this technology in the current medical market. The investigation also included a review of: product specific pricing, cost-benefit assessment, SWOT analyses, FDA regulations, insurance coverage and product licensing requirements.

Analysis has shown that, even with the limited scope of research completed to date, that Microthread technology has a promising future. The inventors of this technology should act quickly to seize upon the opportunities identified in this paper to promote the use of Microthread technology in research and in the medical industry. The inventors should develop a detailed action plan that includes: publishing informative articles in medical periodicals and research journals, a detailed development plan to
enhance the manufacture of Microthreads, map out the most appropriate route to clinical trials and investigate potential vendors to help in the development of a Microthread delivery system that is minimally invasive.

It is critical that the inventors secure legal aid to ensure they are in a position to grant licensing rights of this technology to medical professionals, researchers and commercial vendors as business opportunities present themselves. This, more than anything, may provide the fastest avenue to success for this new and exciting technology.
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I Introduction/Problem Statement

A myocardial infarction, commonly known as a heart attack, is a result from the death of cardiac myocytes (heart muscle cells). This tissue death is due to a deprivation of blood, nutrients, and oxygen to the cells caused by a blocked coronary artery. This blockage can be caused by: an inflamed vascular wall placing additional stress upon the arteries, plaque build-up, or a blood clot restricting blood flow to the heart. Deprived of vital resources the cardiac cells die, leading to drastic changes in the property of the tissue. As time wears on, the once healthy heart muscle is replaced by necrosed tissue which resembles scar-tissue. This tissue is much more rigid with limited contractile properties, is very thin and much weaker than the rest of the heart. The damaged tissue can lead to serious complications and death. It is assumed that if infarcted tissue is repaired it will regain the functionality of healthy heart muscle.

There are six different classification types of myocardial infarctions that a patient may suffer from, as shown in Table 1, provided by the American Heart Association. The resulting tissue-death can be categorized in one of four ways:

- microscopic focal necrosis
- small focal necrosis <10% of the left ventricular (LV) myocardium
- moderate focal necrosis 10-30% of the LV myocardium
- large focal necrosis >30% of the LV myocardium

These classifications apply to all locations where a myocardial infarction may occur in the heart. Once the tissue is dead (and if the patient survives) then the damaged cells will begin to ‘heal’, leaving scar tissue as the remnants that replace the previously healthy tissue.
Myocardial infarctions are a category within the larger group of cardiovascular diseases (CVD) which is the leading causes of death in the United States today. Researchers endeavor to create a device and/or method that will effectively treat or eliminate this detrimental disease. Currently, the concept of treating the cause of cardiovascular complications rather than the effects is dominating cardiac research. Treating the cause of a malady can reduce or eradicate all the effects produced by the illness.

Worcester Polytechnic Institute Professors Pins, Gaudette and Rolle patented a new biomedical scaffold known as Microthreads, a platform technology with direct
relevance to the cardiac market. A Microthread is approximately the size of one strand of human hair, and can be constructed out of collagen or fibrin (naturally occurring proteins within the body). These threads can then be seeded with therapeutic cells on the exterior surface. The cell-seeded threads can be bundled in groups of ten, threaded through or attached to a surgical needle and sutured into infarcted heart tissue. There are currently three different ways in which the Microthread technology can be sewn into the heart. The first involves sewing the cell-seeded threads along the outer perimeter of the infarction. The second is to sew two halves of an infarcted region together using the threads, creating a seam that promotes vascular regeneration. The third option is to create a weave of threads through the necrosed tissue, forming a living patch over the affected area.

Though this is an intriguing new technology with a multitude of positive attributes, there are still many factors that must be considered. This paper focuses on answering the question of whether or not Microthreads are worth pursuing. This was accomplished by analyzing their ability to stand up to the competition, receive regulatory and insurance approval, as well as having a chance to succeed against usual product challenges. Through the use of research, comparisons and analyzes the author of this paper gained a deeper understanding of the market and competition to determine the worth of Microthreads. This paper investigates the use of Microthread technology in healthcare from the stakeholders’ point of view. The investigation included a review of competing therapies, government and industry regulations and overall cost. This report addresses the hurdles Microthread technology must overcome and provides recommendations in order to become successful.
II Methods/Procedures

In order to determine the viability and practicality of Microthread technology in today’s medical industry, a comprehensive analysis of this new technology’s overall feasibility, cost and potential market position must be accomplished. To gather the necessary background data and information on Microthreads and competing technologies a comprehensive review of available literature and interviews with industry experts was conducted.

- Literature research
  - Scientific articles
  - Patents
  - Regulatory Agency documents
  - Various legal documents
  - A range of representative sample of insurance plans from industry leaders

- Interviews
  - Professionals in their respective fields
    - Cardiac
    - Insurance
    - Microthread technology

The information gathered during this effort has been compiled and evaluated to provide valuable comparisons and analyses that may be used to establish where the Microthreads fall within today’s medical market. A SWOT analysis to evaluate the technology’s strengths, weaknesses, opportunities and threats within the cardiac market; and a Cost-
Benefit analysis will give a straightforward look at the opportunities that exist with this technology.

The review of Microthread technology presented here is limited to and emphasizes cardiac care with open heart surgery as the baseline corrective medical procedure, unless otherwise stated. This was done to leverage current research work being conducted by researchers at WPI; their emphasis has been in the area of cardiac care.

III Results

Based on the assumption that FDA approval for the use of Microthread Technology will be obtained and that a HCPCS code is acquired, this review has shown that a strong market potential exists for this technology in the cardiac care arena. This argument is based on the following:

- Current population who have suffered a myocardial infarction\(^2\): 8.1 million
  - People who will have their first infarction this year\(^4\): 600,000
  - People who will have a recurrent infarction\(^4\): 320,000
- Total inpatient hospital costs for CVD in 2005: $71.2 billion\(^4\)
- Estimated Direct and Indirect cost of CVD for 2008: $448.5 billion\(^4\)

While there are a substantial number of patients in this market, the exact number of people who would benefit from this technology is not known. This is due to the fact that there is no numerical data on the breakdown of people who suffer from acute, moderate and/or severe myocardial infarctions. The data is also subject to the quality of patient life, since it is variable by age, physical health and mental health. Despite these
unknowns, there are many who can benefit from this procedure. If this technology is used during open heart surgeries, then it could have been utilized in approximately 469,000 operations in 2005. The market for this device will be even larger once it is perfected for minimally invasive procedures. This would not only allow it branch into the cardiology and stent market, this would allow for patients who otherwise rely on medications and rehabilitation to treat their symptoms to increase their quality of life.

This product differs greatly from products on the market currently and in known development. Unlike many of its competitors, Microthreads have the potential to be used in two of the main heart care arenas: open heart surgeries and minimally invasive procedures. In addition to this, Microthreads technology has the ability to effectively place cells within infarcted tissue and allow the cells to regenerate.

Definitive pricing is not known for many of the developmental technologies due to their proprietary nature and a need-to-know basis. It is safe to assume that Microthreads are likely to be less costly than their major competitors based on their anticipated ease of use and manufacturing process. The developmental cost of Microthreads is far less than the development of most technologies and utilizes materials from readily available resources. This technology can be integrated into pre-existing procedures, such as open heart surgery or cardio-endoscopy, allowing for the threads to be more cost-effective in the long run.

Microthreads have the potential of virtually unlimited application within living organisms. The cardiac applications examined here are merely the foundation that will define Microthreads’ capabilities and uses since they are, in essence, a platform technology. While the myocardial applications appear to be a highly beneficial area to
investigate, once the market has been established, this product can be used to treat other diseases as well. Microthread technology could be applied to improve patients who suffer from: multiple sclerosis, ligament damage, severed spinal chord, stroke, chronic wounds and liver or kidney damage. This will allow for a continuous growth in the life cycle of the Microthread market.

The benefits of Microthread technology outlined in this paper are evidence of this products likelihood to succeed in the medical market today and in the future. By treating the cause of the problem rather than the effects, Microthreads can improve the quality and length of life for many people who suffer from myocardial infarctions. Not only does it treat the immediate problem, it helps eliminate additional heart damage that can be caused by strain placed on the healthy tissue. This will likely mean fewer subsequent hospitalizations, lower cost to insurance companies and patients, and an enhanced life for those who have suffered infarctions. With the low projected costs, the strong market need, and the benefits of this medical treatment, Microthread technology is a worthwhile pursuit. The key to the success of the threads remains with the continued improvement of the technology while pursuing the market requirements simultaneously.

In order to advance the use of this new medical treatment, it is this author’s opinion that greater focus needs to be applied within both the marketing and engineering/research arenas. The architects of this technology must generate a business plan for the future marketing of their device. They must use their knowledge of where the product development is currently to create milestones and to begin the informative process of the FDA regulatory board in addition to filing for a HCPCS code for their device if their choice is to actively market this product. At a minimum, licensing
agreements must be investigated and pursued to ensure the intellectual property for this technology is protected. Once licensing has been arranged, the technology will be available to other researchers in various medical fields where seeding of regenerative or stem cells require the unique properties of Microthreads for implantation. If this is not accomplished in a timely manner then the market release and clinical trials of this product could be exposed to unacceptable delays.

IV Discussion

IV.1 MEDICAL & MICROTRHEAD TECHNOLOGY OVERVIEW

IV.1.1 Medical Review of Myocardial Infarctions

As discussed earlier, one of the main causes of cardiovascular problems is infarcted heart tissue. The term infarcted corresponds to tissue death due to a lack of blood, oxygen and nutrients. Deprived of vital resources the cells die, leading to changes in the property of the tissue. As time passes after a heart attack, healthy heart muscle is replaced by necrosed tissue which resembles scar-tissue. This tissue is much more rigid with limited contractile properties; it is very thin and much weaker than the rest of the heart\textsuperscript{5}. The damaged tissue can lead to serious complications and death if untreated. Anecdotal evidence points to the assumption that if infarcted tissue is repaired it will regain the functionality of healthy heart muscle.

IV.1.1.1 Number of CVD/Myocardial Infarction cases in the US

The numbers of people who suffer from cardiovascular disease and/or myocardial infarctions (MI) indicate how large the target market is for Microthreads. In 2005, 80.7 million people had been recently diagnosed with or were already living with some form
of cardiovascular disease. 8.1 million of these people suffered from a Myocardial Infarction\(^2\). It is projected that in 2008 that an additional 600,000 people will suffer from a new heart attack, while 320,000 will experience a subsequent attack\(^2\). With so many people affected by this disease, and thousands more being diagnosed with this disease everyday, the market potential for this product continues to grow.

**IV.1.1.2 Death Rate**

Cardiovascular disease (CVD) is the number one cause of death in patients with chronic disease in the United States\(^1\). In 2005, CVD accounted for 35.2\% of all deaths in the United States. This percentage has remained fairly constant over the years. Approximately 2400 Americans die from CVD every day (876 thousand people every year), and 32\% of these deaths occur in people younger than 75. Of these CVD related deaths, 156.8 thousand people died annually from myocardial infarctions\(^4\). This is a small fraction of the total number of people who have suffered from a myocardial infarction, making up only 2\% of the total patients who experienced a heart attack.

**IV.1.1.3 Survival Rate**

Currently, there are roughly 7.9 million Americans who have survived a myocardial infarction. Many of these people return to relatively normal lives and work within two weeks to three months after the attack depending on the severity of the infarction. Typically patients make some concessions in their daily routines as they adapt to physical changes brought about by a heart attack and are usually advised to undergo a rehabilitation regimen to learn how much strain is safe to put on their heart.
Rehabilitation normally begins as soon practicable after the heart attack and continues through the heart’s healing process.

IV.1.1.4 Quality of Life

The changes in the quality of patients’ lives after a myocardial infarction can range from relatively minor to severe based on both the physical damage done to the heart and the psychological trauma caused by the attack on the patient. Physical ability can be limited due to the extent of the infarcted tissue. If the injury is small then it often is not noticeable to patients. Larger areas of infarcted tissue greatly reduce the heart’s functional level and limit the amount of physical work a patient can perform. This limitation is the result of additional strain placed on the non-infarcted tissue compensating for the decrease in overall heart muscle. In some cases this stress is too great for patients to return to their previous lifestyle. Increased stress on the heart also tends to increase fatigue in many patients, as the heart works harder to keep up with day-to-day activities. Medications such as digoxin increase the strength of the non-infarcted tissue and allow these patients to better perform physical activities though they may be limited in what tasks they can perform.

After a heart attack, patients are prone to feel a wide range of emotions for two to six months after the incident. The most common emotions for patients to experience are depression, fear and anger. It is considered normal to experience these emotions directly after the event, but these feelings should subside. If the depression, fear and anger continue it can severely affect the quality of patients’ lives. The fear and general apprehension of having another heart attack can cause a patient to avoid both the normal activities and rehabilitation that would otherwise improve their chances of avoiding
further attacks. Depression is considered one of the most dangerous side effects due to the multitude of areas it affects and the fact that it can remain hidden. This emotion can interfere with sleeping, eating, self-esteem (feeling worthless) and can create thoughts of suicide. It is very important for patients who experience these emotions to talk to their families and their healthcare professionals. The only way their quality of life will improve is if they take active steps to address these emotional problems.

IV.1.1.5 Cardiac Rehabilitation

Following any major cardiac episode patients are encouraged to enter into cardiac rehabilitation. This is a medically supervised program which includes a regimen of heart medications as well as physical therapy to improve the overall health of the patient and diminish physical limitations. A study conducted by the Division of Cardiology, Ospedale Maggiore di S. Giovanni Battista, di Torino, Italy, showed that “[rehabilitation participants] had a significantly higher work capacity, a higher double product reached during the stress test and lower triglycerides… patients were more symptom-free (44% against 30%)… 6.1% of the R[ehabilitation] group and 11.2% of the C[ontrol] group developed a new myocardial infarction.” This indicates that there is a 45.5% decrease in the recurrent heart attacks in the rehabilitation group compared to the control, a significant difference in overall health.

Despite such positive results, rehabilitation programs tend to go unused by a significant portion of heart patients. Women are 55% less likely than men to participate in these programs, and older patients are less likely to participate than their younger counterparts. Patients over the age of 70 have a participation rate of 32%, a relatively low percentage given the predominance of the disease in this age group. In the 60-69
year old group, 66% of patients are actively involved in rehabilitation; and 81% of patients younger than 60 participate in the rehabilitation programs. While the involvement in all age groups is far less than it should be, of all the age groups only 17% complete the entire rehabilitation program.

Factors that affect participation:

- **Costs:** Rehabilitation starts the moment a patient enters the hospital with a cardiac episode and continues for three to six months afterwards. Rehabilitation involves a large number of medical professions and time consuming medical appointments and therapy sessions. The bills can become very steep and older patients are not always able to afford treatment. This is particularly true if insurance does not cover all aspects of the rehabilitation effort. Medicare covers most of the costs, but requires patients to pay $135/yr for the coverage, in addition to paying 20% of Medicare approved amounts. To older patients with a limited income, this can make pursuing cardiac rehabilitation unrealistic. Learning how to function after a heart attack without experienced medical help can be far more appealing than the stress from ever mounting medical bills. Any procedure that could cut these costs would likely be very appealing to the elderly.

- **Patient psychology:** Patients fall into extremes when it comes to reasons for not participating in the program. Studies have found that patients fall into a wide range of categories:
  
  - Ruled by fear - This group typically believes rehabilitation may trigger a further myocardial infarction or incident.
o All Knowing - These patients believe they do not need the therapy because they ‘know” exactly what their limitations are. They do not need to waste the time and money as they already know how to handle their situation.

o Post-MI depression - This is very common creating a “what does it matter” mentality towards every aspect of their recovery. If it is not diagnosed, they may fall out of treatment completely.

- Patient gender: The highest incidence of myocardial infarctions occurs within the ranks of the elderly. Of this group, men tend to pursue rehabilitation more frequently than women. Conventional wisdom suggests that elderly men pursue rehabilitation more frequently because their spouses are alive to provide support. Women, on the other hand, live longer than their male counterparts and are more likely to be on their own when illness strikes. This lack of spousal support may explain the decreased frequency of women undergoing cardiac rehabilitation.

**IV.1.1.6 Infarcted Tissue vs. Healthy Tissue**

The heart has three distinctive layers of cardiac muscle fibers: the endocardium (a thin inner layer of epithelial tissue), the myocardium (a middle layer cardiac muscle) and the epicardium (a thin external layer of epithelial tissue)\(^\text{11}\). For the purposes of this analysis, the application of Microthread technology focuses on the myocardium. The cardiac muscle fibers within the myocardium are arranged in a spiral pattern around the circumference of the heart. The ventricular muscle contracts and shortens the diameter of the ventricular chambers as the apex is simultaneously pulled upward, directing the blood toward the openings of the heart’s major arteries\(^\text{11}\). This wringing effect creates the heart
beat. The beat of a healthy heart is regulated by a series of electrical impulses that causes the cardiac muscle fibers to contract and the heart to pump efficiently. These electrical impulses are regulated by two nodes, the sinoatrial node (SA node) and the atrioventricular node (AV node). The cue to start the contraction is sent from the SA node down to the AV node, the signal is then sent down a tract of specialized cells, known as the Bundle of His, located in the interventricular septum (the tissue that separates the right and left ventricles). The Bundle of His branches off into small fibers (known as Purkinje fibers) that extend throughout the ventricular myocardium, allowing the signal to travel throughout the muscle fibers, causing the ventricular contractions to begin.

![Figure 1: Healthy Heart vs. Infarced Heart](image)

*Figure 1: Healthy Heart vs. Infarced Heart*

*Left: Healthy Heart Muscle*

*Right: Infarced Heart Muscle, off-white strip on the upper section of heart muscle is infarced tissue.*

When the muscle is deprived of oxygen and blood, it will die forming an area of necrosed tissue on the heart. This necrosed muscle will slowly be replaced by scar tissue, composed primarily of fibroblasts and type III collagen. Collagen type III is a fibrillar collagen that is found in many tissues, especially within blood vessels, and it plays a major role with tissues that exhibit elastic characteristics. While this type of collagen is
present in many elastic tissues, collagen type III has minimally elastic properties. “The infarced regional elasticity [of the scar tissue] depends on the ratio of fibrous to muscular tissue and the density of the collagen cross-links [that develops as the infarction heals]”\(^\text{14}\). This makes the area of the infarction very weak and the stress of pumping blood further fatigues the scar tissue over time, so that the infarcted area may grow further decreasing heart function. Infarcted tissue is not only much more brittle than the muscle that it replaces, it is also much thinner. A visual example of this damage can be seen in Fig.1. The infarcted region of the heart can continue to thin over the course of a patient’s life as the mechanical stresses of the heart bear on the scar tissue.

### IV.1.1.7 Open Heart Surgery

To be considered as a candidate for this surgery, a person must suffer from one or more of the following conditions: congenital heart disease, damaged or diseased heart valves, severe heart disease that requires a heart transplant or severe blockage of the arteries that necessitates bypass surgery. In addition to this, the patient must be healthy enough to withstand the stress of a major surgery. These patients must be willing to take the risk of complications that result from open heart surgery as well as the grueling rehabilitation process that follows\(^\text{16}\).

Open heart surgery is an extremely invasive procedure with serious implications. Complications can range from mild to life threatening. The most basic complications are post operative bleeding, infection, numbness, and nausea. Serious complications include stroke, heart attack, graft failure, pneumonia, lung or kidney failure, nerve or organ damage and death. In 2006, there were a total of 694,000 open heart surgeries in the US, 448,000 of those were bypass surgeries which closely relates to myocardial infarctions\(^\text{17}\).
IV.1.2 Review of Microthread Technology

IV.1.2.1 Microthreads

The premise behind Microthread Technology is to provide a support structure, a scaffold, which will permit therapeutic cells to be anchored to damaged tissue with the intent of promoting cell growth and regeneration of healthy tissue within the body. Patented in 2007-2008, Microthreads is a new biological technology that has been developed by Professors Pins, Gaudette and Rolle from Worcester Polytechnic Institute. A Microthread is a long biopolymer strand constructed out of either fibrin or collagen and is approximately the diameter of one strand of hair.

![Figure 2: Unseeded Microthreads, Close Up](image1.png)

![Figure 3: Seeded Microthreads, Close Up](image2.png)
The biopolymer threads are seeded with human mesenchymal stem cells (hMSCs) cells along the exterior surface (Figs.2-3), or in a co-culture system that is currently being tested. For myocardial applications, the threads are bundled into groups of ten and looped through the eyelet of a needle or attached to a cellular sheath. The Microthread bundles are then sutured in and around the infarcted area of the heart (Fig.4). In addition to being used as simple sutures around small areas of infarcted tissue, it is envisioned that, in the future, Microthreads can be woven over a larger infarction area \(^{19,20,21}\).

Ultimately the bundle will be covered by an outer sheath that will reduce or prevent shearing of base cells and tissue as the Microthread bundle is passed through the myocardium. The outer biodegradable sheath and Microthread bundle are left in the heart to regenerate tissue (seen below in figure 5), while the needle and excess threads are cut off and removed.

1 – The Myocardium
2 – Microthreads with Sheath
3 – Surgical Needle
4 – Excess thread and needle removed
Animal testing of Microthread technology to evaluate the basic mechanical properties of the threads and gauge their overall effectiveness is ongoing. Professor Gaudette sutured a bundle of Microthreads into a living rat’s heart as part of the investigation. This was accomplished using the same or similar procedures and protocols that are used for human open heart surgery. Figure 7 shows the bundle of Microthreads as it passes through the heart wall attached to the surgical needle.

Professor Gaudette found that the threads were easy to use and did not break under the stresses of suturing. In addition, the threads remained anchored in the heart and
appeared to stimulate angiogenesis (formation of new blood vessels). The exact amount of tissue the threads can repair is still unknown, but will be explored as animal testing continues in larger animals. The sutured threads can be seen on the outer surface of the Rats heart along with the beginning of angiogenesis in Fig.8.

Figure 8: Rat Heart Sutured with Microthreads

White arrows are pointing to the Microthread sutures

IV.1.2.2 Microthread Technology

Microthread technology offers numerous potential benefits to greatly improve patients’ lives. The simple geometry and flexibility of Microthread fiber will provide cardiologists and surgeons a great deal of latitude in their use and application. Microthreads have few limitations beyond the mechanical strength of the basic biopolymer fiber. The composition of the threads is a key attribute that differentiates it from anything on the market today. By using collagen and fibrin threads, scaffolding which in the past has been overlooked due to structural properties, the creators have formed biodegradable threads from naturally occurring proteins. This property lowers the chance of a negative immunoresponse from the patients.
As stated earlier in this paper, Microthreads are in essence living threads, seeded with therapeutic cells along the exterior surface, which can be anchored to damaged tissue to promote cell growth and stimulate angiogenesis. These threads can be sutured into the heart utilizing a range of medical methodologies. Suturing single threads and thread bundles along the edge of the infarct can promote cell growth along the perimeter the repaired area. Weaving a mesh of Microthreads, through and over the infarcted heart tissue, can create a living patch within the heart wall that can stimulate cell growth from the inside and out. In instances where medical procedures require wholesale removal of heart tissue as seen with a Batista Procedure, Microthread technology could be utilized to join the bisected heart together while promoting the growth of cells between the two halves.

Minimally invasive procedures encompass the future cardiac applications of this technology. Cardiac endoscopy and similar medical procedures could be used to deliver the Microthreads to the affected areas of the heart. Currently, endoscopes with diameters of 5mm and 3mm are utilized for sewing heart valves and coronary arteries via small incisions in the thoracic cavities\textsuperscript{22}. These procedures would allow the Microthreads to be sutured into failing heart tissue with minimal stress on the patient. Minimally invasive procedures similar to endoscopy also have the advantage of lowering patients’ pre-qualifications requirements for surgery because they are much less taxing on the body. Medical procedures to place Microthreads in the heart would likely be conducted on an outpatient basis, requiring approximately one full day to complete with no overnight observation required except in special cases.
Enhanced placement of therapeutic agents during major heart surgeries and anticipated use of minimally invasive procedures to treat less complicated heart problems can increase the range of patients that can benefit from new cardiac therapies using Microthreads.

IV.1.2.3 Microthread Fabrication

Fibrin Microthreads are created through a co-extrusion process which involves solutions of fibrinogen and thrombin. The fibrinogen is dissolved in a HEPES buffered solution and the thrombin is a stock solution in HBS. The fibrinogen and thrombin solutions are then warmed to 37°C and placed into separate 1mL syringes. These solutions are coextruded through a blending applicator tip which connects both syringes. As the solutions are combined, they are extruded through a polyethylene tubing (0.38mm in diameter) into a bath of HEPES at room temperature. The threads are then hand-drawn through the bath. The threads are removed from the bath and air dried under the tension of their own weight. The Microthreads are then stored at room temperature in a desiccator until they are used. When the threads are needed, they are rehydrated in PBS, sterilized in 70% isopropyl alcohol and then rinsed in sterile PBS. The sterilized threads are then seeded with cells (typically hMSCs) in media and incubated\textsuperscript{19}. 


Collagen Microthreads are created through a similar process. Rather than co-extrusion, collagen Microthreads are singularly extruded through a 0.38mm diameter polyethylene using a syringe pump. The collagen threads are then extruded into a bath of fiber formation buffer, then moved into fiber incubation buffer and finally into distilled water. The threads are then air-dried under the tension of their own weight and seeded with cells (hMSCs) as the fibrin threads were\textsuperscript{19}.

**IV.1.2.4 Future Microthread Manufacturing Methodology**

Microthreads are currently manufactured in less than a day, by hand and in small batches, using a portable extrusion device created by Professor Pins of WPI. Microthreads are manufactured on location; the threads are not prefabricated at this point due to concerns with maintaining the threads in a sterile environment. It is also unclear as to how much time the adding a patient’s own adult mesenchymal stem cells to the Microthreads would affect the production time of the threads. This uncertainty is due to the early stages of the production of the threads and will improve as more research is conducted as the project moves forward. At this time the team has not considered onsite fabrication and seeding of the threads\textsuperscript{20,21}.
When clinical trials occur, the Microthreads will have to be manufactured on location. Eventually the manufacturing process will progress to a contained, sterilized environment that will still require the human touch to take the threads out of the buffer solution. The creators of Microthreads hope to one day utilize a bioreactor to hold Microthreads and seed them with a specific patient’s cells.

**IV.1.2.5 Packaging**

In the long run, Professor Pins hopes to create a bioreactor that would be capable of sustaining large quantities of Microthreads that could be seeded with the correct type of cell and then shipped to the respective locations\(^{20,21,23}\).

**IV.1.2.6 Shelf-life of Microthreads**

While this has yet to be tested or characterized at this point, the team has stored threads for at least two weeks in their laboratory and used them later with success. At this point the timeframe for the optimal effectiveness of the microthread in its life has yet to be established or researched\(^{20,21,23}\).

**IV.1.3 Follow-on Microthread Research**

Biopolymer Microthread technology is in its infancy. As such there are still many medical and technical issues that must be managed and addressed before the product will be ready for the medical market. The areas of concern that will be addressed through research and further animal testing include:

- Investigate the limitations of Microthread therapies –
  - Effectiveness of Microthread(s) to provide various therapeutic strategies to infarct damage.
• Effectiveness of seeded Microthread(s) to regenerate cells and tissue in infarcted areas of the heart.

• Evaluate complications from the use of Microthreads including the potential for developing scar tissue.

• Investigate the biological mechanisms that inhibit repopulation of cells in a seeded area and identify inhibiting factors.

• Develop a biodegradable sheath to house Microthread bundles that will prevent sheering of the tissue and basal cells.

• Develop or modify existing minimally invasive medical procedures to introduce Microthread based therapies to affected areas of the heart.

• Investigate to determine the immunoresponse of humans to the bovine collagen.

• Investigate methods to produce and manufactured Microthreads on a large scale in a sterilized environment.

IV.1.4 Other Microthread Marketing Opportunities

While the cardiac market is very large and can benefit greatly from Microthreads, there are many other disease segments within the health market that can potentially be treated with these threads. This is due to the fact that Microthreads are a platform technology, since the scaffolding can remain the same and the cells that are seeded along the exterior can be changed to support regeneration of various tissues or cells and therapeutics agents.

Once the technology has been fully developed and the cardiac market successful infiltrated, it is this author’s opinion that this product can then be extended to many opportunities including:
Multiple Sclerosis (MS) – A chronic disease of the nervous system that slowly breaks down the nerves and nerve tissues of the patient. This is an unpredictable disease that results in very difficult and painful symptoms that include: blindness, numbness, tremors and fatigue. In the nervous system the nerve cells are protected by a myelin sheath made up of oligodendrocytes. MS attacks the myelin sheaths, which surround the nerve cells, leaving the nerve completely exposed. It may be possible for surgeons to use Microthreads to deliver pre-oligodendrocyte cells to nerve rich areas and promote growth of myelin sheaths, reversing the damage that causes MS.

Ligament Damage – Any ligament that is torn throughout the body could be repaired using Microthreads. A typical ligament is 90% collagen I, 9% collagen III and 1% fibroblasts. By varying the method of bundling and seeding of Microthreads, biomedical engineers and physicians could manufacture replacement ligaments for patients, eliminating the need to transplant ligaments from other parts of the body.

Spinal Chord Injury – A spinal chord injury is devastating. The surrounding tissue and resultant neuron death has been an insurmountable problem for doctors and surgeons. In the future it may be possible to adapt Microthreads technology to repair the tissue surrounding the chord as well as delivering regenerative cells to improve or regenerate neurons and their functions. Direct delivery of therapeutic agents and regenerative cells could help reduce paralysis and pain.

Stroke – The most common type of stroke is ischemic and occurs when arteries are blocked by blood clots, fatty deposits or plaque build-up. Approximately two
million brain cells die every minute when an area of the brain is deprived of critical blood flow. This poses a high risk of permanent brain damage, disability and/or death. The necrosed brain tissue resulting from a stroke may be treated similarly to infarcted heart tissue in the future. While the functions and abilities that were controlled by the area of the brain affected during the stroke are lost permanently, a procedure with Microthreads could deliver regenerative cells through minimally invasive routes or during brain surgery.

- **Chronic Skin Wounds** – Chronic wounds are typically very painful that do not heal. There are three major categories of chronic wounds include: venous ulcers, diabetic ulcers and pressure ulcers (bed sores). Microthreads may be introduced by the surgeon to help the patient’s body heal with regenerative cells and the additional support of angiogenesis. Utilizing a woven Microthread structure it may be possible to cover and close the wound, effectively creating a living patch of healthy tissue. The thread structure would likely be seeded with therapeutic agents that reduce infections and promotes healing.

- **Liver/Kidney/Organ Damage** – Like the cardiac therapies described earlier in this paper, Microthread technology may be utilized to regenerate necrosed or injured tissue in the liver, kidney and other organs. Again, utilizing minimally invasive procedures, Microthreads could help repair tissue to reverse the effects of disease such as cirrhosis of the liver or may be used to reverse the effects of physical trauma (a result of a car accident or other physical violence) on the organ as well.
IV.2 COST DRIVERS AND ANALYSIS

IV.2.1 Stakeholders in the Cardiac Industry

IV.2.1.1 Cardiologists

Cardiologists are physicians who identify and treat diseases of the heart and blood vessels. Typically the cardiologist is the first medical professional a patient will see for heart related conditions and concerns. The cardiologist is highly trained to diagnose heart related illness through review of medical history, examinations and routine tests. Cardiologists regularly perform minimally invasive procedures that include cardiac catheterizations (inserting balloon catheters into the coronary arteries) as part their patient evaluation. This ability to proficiently perform minimally invasive procedures, that include cardiac catheterizations, may be leveraged to perform similar procedures utilizing Microthread technology.

Market Benefit to the Cardiologist – Increased client base.

Cardiologists will be able to perform Microthread implantation eliminating the need to send patients/clients to cardiac surgeons. This will enhance the cardiologists’ patient/market share.

IV.2.1.2 Cardiac Surgeons

Cardiac surgeons perform intense, invasive procedures on the heart and/or great vessels. Surgery is performed to treat complications of ischemic heart disease (for example, coronary artery bypass grafting), correct congenital heart disease, or treat valvular heart disease created by various causes including endocarditis. Microthreads therapy offers the surgeon a new tool to effectively seed regenerative cells, graft heart patches and apply medical therapies to the myocardium during open heart surgery. If
testing confirms that microthreads have sufficient strength, it may be possible for the surgeons to replace the sutures currently used during surgery with seeded Microthreads. This offers the possibility of faster and more complete healing of the patient’s heart tissue following surgery.

Market benefit to the Cardiac Surgeon – Increased client base.

Microthread technology will likely to decrease the “low risk” patient/client base. This includes the procedures performed by Cardiologists.

Due to the less invasive nature of this technology, cardiac surgeons will be able to perform procedures on high-risk patients that currently don’t qualify for surgery. The technology has the potential to improve the overall quality of the surgery/service provide by the surgeon. Since the Microthread technology may increase the life span of the patients, the surgeons would benefit monetarily from longer or more fulfilled long-term surgery follow-up appointments.

IV.2.1.3 Patients

Patients, as the end users of these Microthread therapies, have the most to gain with this new technology. Through the use of minimally invasive Microthread technology, patients will have the potential for decreased downtime from surgery, faster healing and increased heart strength and functionality.

Market benefit to the Patient – cost and time savings.

It is anticipated that the overall quality of the patient’s/client’s life will increase with a decrease in overall cost and effort.
IV.2.1.4 Biomedical Engineers

Biomedical engineers invent, expand and market new medical technologies like Microthreads. With the successful approval and use Microthread technology by the medical sector, further use and expansion of this field is anticipated. Currently biomedical engineers envision that the use of Microthreads, as cellular scaffolds, hold limitless possibilities for rehabilitation in the human body. Threads woven together to form patches, could be seeded with base cells, in essence creating living patches. These “living” patches could then be layered with other “living” patches until an entire area of organ tissue could be grown. This could ultimately lead to the regeneration of organs by creating scaffold of living tissue.

Market benefit to the Engineer – high growth potential.

This is a new industry with promising potential.

IV.2.2 Cost Review and Analysis

IV.2.2.1 Cost of Microthreads

In order to be successful in a competitive market, it appears that Microthreads must be manufactured and utilized for under $363. This value is based on the results provided in Table 2, which explores the cost of medicinal treatments over the course of a patient’s remaining life. Table 2 was derived from the medicinal cost matrix (Appendix 3) and has the three top drug combinations that the author found to be most commonly used by cardiac rehabilitation patients: Digoxin, ACEI and Beta Blockers.

The dosage along with the brand of the drug combinations aims to show the minimum, mean and maximum pricing for each medication. For example, in the Digoxin and ACEI section Lisinopril 10mg represents the minimum cost for an ACEI, while
Captopril 100mg represents the expensive ACEI types and Ramipril 10mg is the average price of multiple ACEI’s. The author did this to give a clear understanding of the medicinal combinations in general, since a matrix with all drugs and dosages would be quite difficult to understand.

Table 2: Medicinal Cost Matrix - Life Expectancy

<table>
<thead>
<tr>
<th>Medication Combinations</th>
<th>Cost per year</th>
<th>Median Survival Years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>7.4¹</td>
</tr>
<tr>
<td>Digoxin</td>
<td></td>
<td></td>
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<tr>
<td>Digoxin 0.125mg</td>
<td>$182</td>
<td>$1,344</td>
</tr>
<tr>
<td>Digoxin 0.25mg</td>
<td>$248</td>
<td>$1,838</td>
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<tr>
<td><strong>Digoxin + ACEI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digoxin 0.125mg +</td>
<td></td>
<td>$398</td>
</tr>
<tr>
<td>Lisinopril 10 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digoxin 0.125mg +</td>
<td>$3,434</td>
<td>$25,408</td>
</tr>
<tr>
<td>Captopril 100 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digoxin 0.125mg +</td>
<td>$962</td>
<td>$7,116</td>
</tr>
<tr>
<td>Ramipril 10 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digoxin 0.25mg +</td>
<td>$464</td>
<td>$3,437</td>
</tr>
<tr>
<td>Lisinopril 10 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digoxin 0.25mg +</td>
<td>$3,500</td>
<td>$25,903</td>
</tr>
<tr>
<td>Ramipril 10 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digoxin 0.25mg +</td>
<td>$1,028</td>
<td>$7,610</td>
</tr>
<tr>
<td>Ramipril 10 mg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table 3: Medicinal Cost Matrix - Life Expectancy ~ Continued

<table>
<thead>
<tr>
<th>Medication Combinations</th>
<th>Cost per year</th>
<th>Median Survival Years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Digoxin + BETA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digoxin 0.125mg +</td>
<td>$290</td>
<td>$2,143</td>
</tr>
<tr>
<td>Metoprolol tartrate 50 mg</td>
<td></td>
<td>$3,011</td>
</tr>
<tr>
<td></td>
<td>$1,670</td>
<td>$12,355</td>
</tr>
<tr>
<td></td>
<td>$746</td>
<td>$5,517</td>
</tr>
<tr>
<td>Digoxin 0.25mg +</td>
<td>$356</td>
<td>$2,637</td>
</tr>
<tr>
<td>Metoprolol tartrate 50 mg</td>
<td></td>
<td>$3,707</td>
</tr>
<tr>
<td></td>
<td>$1,736</td>
<td>$12,849</td>
</tr>
<tr>
<td></td>
<td>$812</td>
<td>$6,012</td>
</tr>
</tbody>
</table>

† Median patient survival years for women 60-69yrs, men 70-79yrs
‡ Median patient survival years for women 70-79yrs
* Median patient survival years for women ≥ 80yrs
# Median patientsurvival years for men ≥ 80yrs

The costs to use these medicines per year in this table were determined based on the average dose per day and the number of capsules usually prescribed to obtain a yearly cost. The price of medication for each individual month was calculated and the total costs for all twelve months were combined to obtain the yearly cost. The yearly cost was then multiplied by the median survival year brackets located across the top of the table. Hospital, physician and other medical costs are not included in this analysis since those costs would be consistently applied across current medical procedures. Patients would incur these medical costs due to their illness regardless of the medications prescribed. The survival years represent the median life expectancy of a patient who survived a heart attack over the age of 60 (figures provided by the AHA). The median years are not listed.
in a numerically ascending or descending order; rather it follows the age groups of patients who have survived a heart attack (shown in key at bottom of the table). To determine the total medicinal costs to a patient, the cost of the medicinal treatment per year was multiplied by the median survival year to arrive at the cost (located in the body of the table).

A review of the table shows that the minimum cost of supplying the heart medication to a patient falls under the use of digoxin (a form of digitalis) for a person surviving two years after their myocardial infarction. Based on this, Microthreads must be manufactured and utilized less than or equal to $363.

**IV.2.2.2 Cost-Benefit Analysis**

To date, $23,400 (in the form of a grant) has been spent on the development of Microthread technology. WPI Professors anticipate that a second grant for $405,000 will be received to allow for scale up and validation of the Microthreads in an animal model\textsuperscript{21}, bringing the total to $427,400. Conservatively, an additional ~$500,000 will be required to complete preliminary research and prepare for clinical studies. Based on this, the preliminary development cost of this devise to estimated to be $1million. This cost of development is low enough to have a negligible effect on the per piece price of Microthreads.

If the purveyors of this product choose to bring the technology through clinical trials, then the developmental costs will increase dramatically. According to Thomson Center Watch, the cost of clinical trials is approximately $25,000 for each patient involved in the study\textsuperscript{25}. If the trials are conducted on 2,000 patients, clinical trials alone
would cost $50 million. The increased cost in clinical trials is great enough to have an effect on the price per piece of the Microthreads.

Assuming the procedure used to implant the Microthreads will be minimally invasive in nature, similar to endoscopy or cardiac catheterization, the average cost for the procedure would be approximately $2500. This is based on the following cost data derived from readily available medical literature:

- The maximum price of manufacturing, use and development costs cannot exceed $363 per thread when averaged over the life of the product
- The price of $624 for hospital and physicians’ services is per day\(^2\)
- The average price of a GI endoscopy is $1,398 \(^2\)

This cost is much lower than current, more invasive, medical procedures that include open heart surgery. Indicating at a high level that the anticipated cost does not outweigh the benefit of this device; showing Microthreads may be a beneficial venture to pursue.

Additional benefits that do not necessarily have direct cost related to them but show a strong potential to benefit the patient include:

- Repairing otherwise useless tissue
- Bringing the heart back to full-working capacity
- Improving the quality of patients’ lives
- Enhancing patient longevity
- Eliminating subsequent hospitalization for recurrent issues caused by infarcted tissue.
To put this all into perspective, a “quality of life” analysis for the cost benefit of this new procedure is included. This is done because “quality of life” is the driving force behind medicine and the medical profession. According to a Stanford Economist, the average value of human life per year is $129,000\textsuperscript{28}. Assuming that two years is the lowest average survival years for any age group, the human quality of life that could be attained is equal to $258,000 which is equal to the benefit that the threads provide. Comparatively, the cost of the Microthreads with minimally invasive applications would be approximately $2,500. The benefits greatly outweigh the cost with a beneficial difference of $255,500.

<table>
<thead>
<tr>
<th>Table 4: Cost-Benefit Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cost</strong></td>
</tr>
<tr>
<td>Microthread Manufacturing and Use</td>
</tr>
<tr>
<td>Hospital and Physician Service per Day</td>
</tr>
<tr>
<td>Endoscopic Procedure</td>
</tr>
<tr>
<td><strong>Total</strong> ≈</td>
</tr>
<tr>
<td><strong>Benefit</strong></td>
</tr>
<tr>
<td>Value Quality Human Life</td>
</tr>
<tr>
<td>x2 (minimal survival years)</td>
</tr>
</tbody>
</table>

\[ \text{$258,000 - $2500 = $255,500$} \]

Benefits greatly outweigh the costs.

**IV.2.2.3 Anticipated Cost of a Microthread**

Using the current production techniques, focusing on the extrusion system and the solutions required to create the threads, the manufacturing cost of the threads can be approximated. Baseline costs for equipment and solutions were determined through the use of online suppliers. Most of the extrusion system has a one time use limit, meaning the costs will be incurred during each production cycle of the threads (as seen in the Table 5).
Table 5: Microthread Pricing

<table>
<thead>
<tr>
<th>Price per Thread without Collagen and Cells</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1mL syringe</td>
<td>$0.16</td>
</tr>
<tr>
<td>Surgical Tubing</td>
<td>$0.11</td>
</tr>
<tr>
<td>1xDMEM</td>
<td>$0.04</td>
</tr>
<tr>
<td>HEPES Buffer Solution (1 M)</td>
<td>$13.81</td>
</tr>
<tr>
<td>Pay for Work Study Student (8hrs)</td>
<td>$72.00</td>
</tr>
<tr>
<td><strong>Total w/out Collagen and Cells</strong></td>
<td><strong>$86.12</strong></td>
</tr>
</tbody>
</table>

Based on the findings and assumptions provided in Table 5, the extrusion system costs will be approximately $86 per use. The cost of collagen and seed cells is not included in this analysis since price varies greatly depending on the type of collagen used, the vendor company, and the size of the Microthread batch. The price of collagen products ranges from $231.00/0.5mg (Bovine Collagen Type III) to $525.00/0.5mg (Human Collagen Type IV)\(^29\). The cost of seed cells (mesenchymal stem cells) poses another pricing challenge, because the specific methods necessary to prepare the patient’s cells (separate basal cells into the hMSCs) for this therapy is unknown.

**IV.2.2.4 Cost Reduction Strategies**

Microthreads have the potential to greatly reduce costs associated with the treatment of myocardial infarctions (MI). The cost benefits will be seen by insurance companies, hospitals, physicians, patients and society in general. The minimally invasive nature of the procedures ultimately envisioned for the application of Microthread therapies will limit the duration of hospital visits for treatment. This will, in turn, reduce the overall cost of the treatment and allow the patient to resume normal daily functions sooner.

Microthread therapies will be administered on an outpatient basis that should be completed in one day. At a cost of approximately $624/day for a hospital visit with physician services\(^26\) included, the possible cost savings become obvious. Since the use
of Microthread technology would require a significantly reduced medical follow-up, months rather than years, further cost saving/avoidance would be anticipated.

The current theory that Microthreads, seeded with hMSCs will regenerate infarcted tissue, will lead to less time needed for cardiac rehabilitation. The patients would likely feel better faster enhancing their desire to work on strengthening their heart, expediting the healing process. Bodo E. Strauer et al conducted an experiment comparing the effectiveness of delivering bone marrow cells to an infarcted area along with cardiac rehabilitation versus standard protocol and rehabilitation. The patients who received the regenerative cells and therapy completed the entire rehabilitation course in three months with significant improvement to their infarcts; while their controlled counterparts remained in rehabilitation for six months with no infarct improvement\textsuperscript{30}.

While this will likely result in a higher rate of patients utilizing and completing cardiac rehabilitation programs (cost to insurers and patients will be higher) the overall cost for rehabilitation will be lower because treatment time will be significantly reduced.

As seen in Table 6, Microthreads will also be less costly then the other competing technologies currently on the market or under development. With the known manufacturing costs, Microthreads can be produced and utilized for less than its primary competitor, the heart patch. While synthetic threads, intravenous and direct injection therapies have lower manufacturing cost, the effectiveness of those treatments are significantly less than the effectiveness of Microthreads technology (refer to Section III.4 of this report).
The cost of producing the Microthreads is likely to decrease as use of the technology grows and the manufacturing processes are streamlined.

**IV.2.2.5 Economic Factors**

From an economics standpoint, Microthreads have a good chance of success. There are currently no true alternates for this technology on the market, although there are competitors that currently aim to treat infarcted heart tissue. Microthread technology can be considered to compliment many medical treatments currently in use and/or proposed for use.

The patient’s perceived “willingness to pay” figures greatly into the overall economic value of this technology. The behavioral economic prospective theory shows that if one were to gauge a person’s reaction to the resultant lose or gain from the same reference point; loss is far more emotionally devastating than the emotional reward from the gain. This is relevant to Microthreads because the devastation of losing heart function will, most likely, outweigh the emotional loss associated with losing a small sum of money, increasing the patient’s willingness to pay for a desirable solution.

The supply and demand curves (Figure 10) for this product show cost will remain relatively constant. This is due to the fact that as time goes by the manufacturing process will be streamlined, allowing the threads to be produced in a higher volume and a lower

<table>
<thead>
<tr>
<th>Cost to Manufacture and Utilize</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Microthreads</td>
<td>&gt; $363</td>
</tr>
<tr>
<td>Direct Injection</td>
<td>Minimal</td>
</tr>
<tr>
<td>Heart Patch</td>
<td>$500 - $1000</td>
</tr>
<tr>
<td>Intravenous</td>
<td>Minimal</td>
</tr>
<tr>
<td>Stents</td>
<td>$52,930</td>
</tr>
<tr>
<td>Synthetic Threads</td>
<td>$36</td>
</tr>
<tr>
<td>Medicinal</td>
<td>$363</td>
</tr>
</tbody>
</table>
cost. This will cause the supply curve to shift to the right. As Microthreads infiltrate the market, their benefit is likely to be seen and demand will increase for the threads as well. This will cause the demand curve to shift to the right as well.

IV.2.2.6 Break-Even Point

An analysis was conducted to determine the break-even point for this product to gage the value of pursuing the development of this technology from a financial standpoint. The analysis was accomplished based on assumptions derived from the cost section of this report. The first break-even point was based on licensing Microthreads to other researchers. The numbers were then calculated as shown below:

![Supply-Demand Curves of Microthreads](image)
Variable Cost per Unit

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Extrusion System</td>
<td>$14.12 / 10 units = $1</td>
</tr>
<tr>
<td>Direct Labor</td>
<td>$72 / 10 units = $7</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>= $8</strong></td>
</tr>
</tbody>
</table>

Fixed Cost

| Development Costs     | $1,000,000                          |

Expected Sales

| 10,000 units         |                                      |

Price per Unit

| $300                  |                                      |

Total Revenue

| $3,000,000            |                                      |

Total Variable Costs

| $80,000               |                                      |

Total Profit

| $1,920,000            |                                      |

Calculating the total cost and total revenue for the number of units produced in increments of 500, it was found that the hypothetical break-even point is at 3500 units of Microthreads.

Table 7: Break-Even Profit Preliminary

<table>
<thead>
<tr>
<th>Units</th>
<th>Fixed Cost</th>
<th>Total Cost</th>
<th>Total Revenue</th>
<th>Profit</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>$1,000.00</td>
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<td>$0.00</td>
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<tr>
<td>500</td>
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<td>$1,028.00</td>
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<td>1500</td>
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<td>$1,050.00</td>
<td>$22.00</td>
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<td>$22.00</td>
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<td>$1,050.00</td>
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</tr>
<tr>
<td>3500</td>
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<td>$3,000.00</td>
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</tr>
</tbody>
</table>
The second break-even analysis takes clinical trials into account. The numbers were then calculated as shown below:

<table>
<thead>
<tr>
<th>Variable Cost per Unit</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Extrusion System</td>
<td>$14.12 / 10 units = $1</td>
</tr>
<tr>
<td>Direct Labor</td>
<td>$72 / 10 units = $7</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>$8</strong></td>
</tr>
</tbody>
</table>

**Fixed Cost**

- **Development Costs**: $51,000,000

**Expected Sales**: 200,000 units

**Price per Unit**: $300

**Total Revenue**: $72,600,000

**Total Variable Costs**: $1,600,000

**Total Profit**: $20,000,000

Calculating the total cost and total revenue for the number of units produced in increments of 500, it was found that this hypothetical break-even point is approximately 150,000 units of Microthreads.31
Table 6: Break-Even Profit with Clinical Trials

<table>
<thead>
<tr>
<th>Units</th>
<th>Fixed Cost</th>
<th>Total Cost</th>
<th>Total Revenue</th>
<th>Profit</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>$51,000.00</td>
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<td>$51,000.00</td>
<td>$51,080.00</td>
<td>$3,630.00</td>
<td>($47,450.00)</td>
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<tr>
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<td>$51,160.00</td>
<td>$7,260.00</td>
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<td>($33,250.00)</td>
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<td>($26,150.00)</td>
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<td>80000</td>
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<td>$29,040.00</td>
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<tr>
<td>90000</td>
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<td>($19,050.00)</td>
</tr>
<tr>
<td>100000</td>
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<td>($15,500.00)</td>
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<td>($8,400.00)</td>
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<td>$47,190.00</td>
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<td>($1,300.00)</td>
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<td>$12,900.00</td>
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<td>$52,520.00</td>
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<td>$16,450.00</td>
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<td>$52,600.00</td>
<td>$72,600.00</td>
<td>$20,000.00</td>
</tr>
</tbody>
</table>
### IV.2.3 Strength, Weakness, Opportunity & Threat (SWOT) Analysis

<table>
<thead>
<tr>
<th><strong>Strengths</strong></th>
<th><strong>Weaknesses</strong></th>
</tr>
</thead>
</table>
| * Delivers cells directly to affected area | * Many unknowns at this point in time  
  - How large of an infarct can it repair?  
  - How well will it work minimally invasively?  
  - Will it create scar-pulling around sutures?  
  - Will there be an immunoresponse? |
| * Made of naturally occurring proteins; will be compatible with human bodies | * Not enough current funding |
| * Biodegradable | * Requires more being done on research and marketing simultaneously |
| * Treats cause of the disease rather than the effects | * No milestone breakdown |
| * Regenerates dead tissue | |
| * Cells can be taken directly from patient; autologous | |
| * Very large market | |
| * High potential for minimally invasive procedures in addition to surgical use | |
| * Nothing else like it on market or in development | |
| * Improve the quality of patients’ lives | |

<table>
<thead>
<tr>
<th><strong>Opportunities</strong></th>
<th><strong>Threats</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>* Ripe market, in need of new technology/treatments</td>
<td>* Changes in FDA regulations</td>
</tr>
<tr>
<td>* Competitors only focus on one delivery system and deliver cells in similar fashions</td>
<td>* Changes HCPCS codes</td>
</tr>
<tr>
<td>* Competitors not as precise as Microthreads</td>
<td>* Competitors creating a substitute for Microthreads</td>
</tr>
<tr>
<td>* Can be used as more than just a thread; can be used to create living patches</td>
<td>* Lack of funding</td>
</tr>
<tr>
<td>* Has future potential as a platform technology in other areas</td>
<td>* Unforeseen issues due to unknowns</td>
</tr>
<tr>
<td>* Good local for clinical testing and launching into market</td>
<td></td>
</tr>
<tr>
<td>* Heart market remaining strong and need is increasing for solution</td>
<td></td>
</tr>
</tbody>
</table>
IV.3 MARKET POSITION EVALUATION

IV.3.1 Myocardial Infarction Market Size

The previous sections gave a high level overview of the potential market for myocardial infarctions. With a current population of 8.1 million people having suffered a MI, 7.9 million survivors, 600,000 more people entering the market each year and 320,000 people suffering from recurrent attacks\textsuperscript{4}, the myocardial infarction market provides a solid niche for Microthread technology. While myocardial infarctions do result in death, the total number of those who have perished due to the infarction pales in comparison to the patients who survive with the damaged tissue. Figure 11 illustrates the potential market size (and need for an effective treatment) based on a breakdown, by percentage, of the myocardial market demographics.

Death due to MI is only two percent of the market. This indicates a potential market population of 98\% that can benefit from the application and use of Microthread technology.
IV.3.2 Competition

IV.3.2.1 Injection Method

Currently, there are three competing methods that support direct injection of therapeutic agents or cells into an infarction or into the surrounding tissue. These include direct intracardiac injection, injection during surgery, and the developmental robotic HeartLander.

The favored method of delivering therapeutic cells is via intracardiac injection, a technique derived from the emergency medical practice of delivering epinephrine to a seizing heart. Intracardiac injection accesses the heart directly through the skin utilizing a needle inserted through the myocardium and into a cardiac chamber. This is performed through one of two standard injection techniques that allow direct access to the heart shown in Figure 12.

![Intracardiac Injection Diagram](image)

**Figure 12: Intracardiac Injection**

Subxiphoid approach, needle is inserted 1cm to the left of the xiphoid process and aimed toward the left shoulder. The locations for the parasternal approach are indicated by the red x’s.
The intracardiac injection method is simple, quick and minimally invasive. This procedure utilizes current practices, techniques and technologies to deliver therapeutic cells directly to the infarcted areas of the heart. The needle and syringe are inexpensive and lead to an outpatient procedure. The therapeutic cells that are delivered to the heart can be autologous. Studies have shown a success rate of 11% of the total cells injected engrafting to the heart wall\textsuperscript{33}.

There are drawbacks to this method of delivering therapeutic cells. The potential complications that a patient may experience from the injection itself include the following: pneumothorax (collapsed lung), coronary artery laceration, myocardial laceration, hemopericardium (blood in the pericardial cavity caused by atrium or coronary artery rupture or the perforation of a ventricle), and perforation of the stomach or liver. It has also been associated with inducing intractable ventricular fibrillation\textsuperscript{30}. While using a smaller spinal needle and the subxiphoid method has minimized these complications, they are still a prevalent problem with this procedure. The insertion of the needle into the thoracic cavity can be quite painful and the adherence of the cells to the heart wall is not assured. After the needle is removed, cells are pumped out through the puncture hole or into circulation, and there is no way to control cell growth and attachment\textsuperscript{34}.

The second type of injection occurs during open heart surgery. Unlike its minimally invasive counterpart, this method is utilized as an additional procedure that can help improve heart function. In this case, the surgeon is able to directly inject cells into the infarcted area due to the access that open heart surgery allows.
Since this is an additional procedure that employs common techniques and tools that are relatively inexpensive, it is safe to assume that the cost of the supplementary method will be minimal. The therapeutic cells utilized can be autologous and the success rate of this method is the same as stated above with the intracardiac injection process. The drawback to this technique is that as an additional procedure and with a success rate that is relatively low, surgeons may feel that it is not worth including this practice in the surgery.

The third method is currently in animal testing and utilizes a robotic device to inject therapeutic cells into the heart. This device is known as the HeartLander, an inchworm-like robot that can navigate around the exterior of the heart. This crawling robot consists of a front and rear body section attached to a flexible tether line which the body pieces glide along to induce movement. The tether connects the HeartLander to tabletop instrumentation that supports the various device functions. Three wires pass through the center of the tether which is connected to an exterior motor that creates locomotion. A vacuum line creates suction that allows for the HeartLander to move by alternating the suction between the body sections. The vacuum pressure is monitored by pressure sensors and is regulated by computer controlled valves. This series of balances ensures that the heart tissue is not damaged by the suction force of the device. There is also an optic endoscope that runs through the tether line and is attached to a computer for visual feedback.
In a retracted state, the robot is 17.7mm (length) x 8.2mm (width) x 6.5mm (height). The length changes as the robot makes its way along the heart due to the retracting and extending of the device’s locomotion. The HeartLander has a 1mm diameter needle channel and a 2mm diameter working port where tools can be deployed to rectify a variety of heart procedures. For myocardial injection applications, a surgeon would advance a needle by hand through the 1mm needle channel and into the infarcted tissue. The surgeon would judge the depth of the puncture by textile sensation and through the visualization provided by the HeartLander technology. The cells would be injected through a syringe located on the exterior portion of the needle\textsuperscript{35}.

---

\textbf{Figure 14: HeartLander and placement on heart}\textsuperscript{36}

\textit{Picture Courtesy of the Carnegie Mellon Robotics Institute}
The crawling robot is placed upon the heart by creating an incision below the sternum and inserting the HeartLander into the thoracic cavity using the subxiphoid approach shown in Figure 14. Once that step is completed, a second incision is made in the pericardium. The HeartLander is inserted into the slit and is put directly on the exterior surface of the heart under the pericardium layer. The robot can then crawl over the heart through the use of alternating suction to the front and rear body sections. The distance between the body sections is created by an external actuator that pushes and pulls upon the tether of the HeartLander.

The therapeutic robot is controlled by a doctor using a joystick and a computer program directly linked to the HeartLander to show the exact location of the technology on the heart. A tracking sensor located on the front body of the robot allows for the real time location of the droid to be displayed on the computer screen at all times.

In vivo testing has been performed in porcine subjects. These studies have shown that the subxiphoid approach is safe for the subjects and has proven the locomotive abilities of the device. During these tests, it was demonstrated that the HeartLander can travel along the anterior and lateral surfaces of a beating heart without restriction. The tests included forward motion, backward motion and turning. No adverse events were noted in the porcine subjects during the trials. After the tests the procine hearts were excised and no epicardial damage was found.

The HeartLander is constructed out of disposable materials that can be hooked up to tabletop instrumentation to be utilized. This allows for the individual units to be replaced for each patient’s surgery. The real-time visualization of the heart with the tracking sensor allows for the surgeon to guide the technology to the exact location they
wish to deliver therapeutic cells. In addition to repairing infarcted heart tissue, this device was created with the objective to improve minimally invasive surgery. The 2mm diameter working tool port can allow the HeartLander to perform a multitude of surgeries once the technology is perfected further.

While exact pricing is not available, it can be assumed that this technology will be costly to use. Even though the HeartLander itself is disposable, the equipment that it is attached to and the procedure that is used will increase the overall cost. It is highly probable that there will be the cost of additional personnel to monitor and run this equipment. Additionally, the software that will be needed to visualize the 3-D model of the heart will be expensive.

Another issue deals with the injection of the therapeutic treatments. As with the other direct injection methods, there is no way to anchor the cells to the affected area. Also, while the surgeons control the depth of the insertion of the needle within the cardiac tissue, testing with dye has revealed that the injection depths averaged from three to five millimeters.

Figure 15: HeartLander CMU test results

Photos Courtesy of the Carnegie Mellon Robotics Institute
If the injection depth is not increased, then it is possible that the infarcted tissue may not be reached. The dye and cell delivery has not been tested in an environment with necrosed tissue yet, so definitive proof is not available.

While all three of these direct injection methods offer unique advantages to the application of cells to damaged heart tissue, every one of the procedures encounter a similar problem: there is no way to anchor the therapeutic agents and cells to the infarcted areas being treated. After cells are injected into the heart and the needle is removed, the majority of the cells are pumped out of the heart into the bloodstream. These methods offer no mechanism to control the cells once they are injected into the heart muscle.

IV.3.2.2 Heart Patch

Heart patches are intended to replace missing and damaged heart tissue. A heart patch is a 3-D scaffold constructed out of synthetic or biologically-derived materials upon which cells are seeded. The scaffolding provides a temporary biomechanical structure for the seeded cells until they are able to produce their own sustainable extracellular matrix. There have been experiments proving that heart patches are feasible although there has yet to be a patch created thicker than one centimeter\textsuperscript{38}.
The patch scaffolds can be created for any size, shape, strength and composition that are needed to repair the infarcted tissue. This permits the researchers to construct heart patches for a patient’s specific needs. These scaffolds can be seeded with autologous cells which is expected to lower the chance of immunoresponse. The tissue that is created with the scaffolds is intended to function as normal heart tissue. This can completely resolve the issue of infarcted and damaged heart tissue by replacing it with healthy, fully functional tissue. Shimizu et al grew rat cardiomyocytes on polymer scaffolds that created thin layers of cells in the form of sheets. Researchers placed four of the cell sheets on top of each other until they fused, and then implanted the fused sheets under the skin of rats for a period of six months. After the six month period, researchers discovered that the heart patch was beating and had been infiltrated with host blood vessels. Zimmerman et al have demonstrated in their experiments that a similar heart patch survives at least 28 days after transplantation into a rat’s heart.

In order for the heart patch to be administered, a patient must undergo open heart surgery. This means the same effects as mentioned in the open heart surgery section apply to this area, as well as potential complications that may come to light as the technology is further developed. Since the damaged tissue is removed and replaced with the patch the chance for complications are increased. The total costs of the procedure will most likely be very expensive. One heart patch scaffold without cells ranges from $500 to $1000 depending on the size and composition of the patch.

IV.3.2.3 Intravenous Delivery

Intravenously introducing cells into the body is done through an intravenous (IV) drip. The drip delivers the treatment via a needle in the patient’s radial vein. The needle is
attached to a plastic tube with a regulator which comes down from a bag that is filled with the fluid used to treat a patient. For cardiac regeneration, a high concentration of cells is introduced to the patient’s body through the IV drip. The cells then travel through the bloodstream to affected area in the heart.

This method is the most minimally invasive of all the competition. Costs will be minimal since this procedure utilizes a current method for delivering fluids into the body and is an in-out procedure. The cells delivered in the therapeutic solution can be autologous to help minimize any immunoresponse. It has been shown in a study by Matthew Pricea that this method also begins to repair tissue in small clusters. However, the same study demonstrated the dangers of this method. Matthew Price and Chung-Chuan Chou found in testing the IV delivery of MSCs to a damaged pig heart that the therapeutic cells attached to and grew in the lungs. The post-mortem examination of the porcine subject revealed “a large bolus of cells in the lung vasculature⁴³", which can create complications. This is caused by the way the therapy enters the body. Since the cells are dripped directly into the bloodstream, the therapeutic cells pass through the lungs and other organs prior to and after passing through the heart. There are no signaling factors that allow the physicians to control where the cells will attach within the body. It
has been found that less than one percent of the therapeutic cells injected into a patient with this method will attach to the heart wall\textsuperscript{44}.

**IV.3.2.4 Balloon Stents**

Stents are used to hold blocked arteries open and increase blood-flow to the heart. Made from tubular meshed wire metal, the stents are collapsed and placed over a balloon catheter. A separate balloon catheter is then inserted into an artery (near the groin, arm or wrist) and advanced towards the heart\textsuperscript{45,46}. A series of x-rays are taken to visualize the clogged heart artery while the balloon catheter is advanced into the heart. Once the catheter-stent reaches the area of blockage, the balloon is inflated and deflated several times to drive the plaque build-up against the arterial wall. The catheter is then removed and the catheter-stent is moved to the afflicted area. When the area has been reached, the second balloon is inflated, expanding the stent which locks in place that forms a scaffold and holds the artery open. The stent stays in the artery permanently and the balloon catheter is removed from the body. The wire stent will be covered in a thin layer of endothelium as the body adjusts\textsuperscript{45,46}.

![Figure 17: Balloon Catheter and Stent Deployed\textsuperscript{47}](image-url)
A recent modification to stents was the addition of a medicated layer on the outer surface of the stent. This medicated layer is intended to help reduce inflammation and the possibility of restenosis (re-blockage) of the artery. The type of medication on the stent varies by the manufacturer, as does the time-release formula of the medication. While a medicated stent theoretically can reduce inflammation, additional medications must be taken by the patient to aid with the healing process. Most patients, whether their stent is medicated or not, are prescribed aspirin or Plavix to help reduce the formation of blood clots in or around the stent.

Stents are minimally invasive and effectively improves the flow of blood. This method is also proven to work specifically for improving the blood flow to the heart.

While stents are capable of bettering the blood flow heart the stents do not have the ability to treat infarcted tissue. Stents can be seen as a preventative measure against infarcted tissue occurring, but once the tissue has reached that point they cannot reverse the damage. Even with the medicated-stents that aid in the repair and health of the arteries fails to affect the heart wall itself. If the medicated gel was replaced with a gel of hMSCs and placed upon the stent, the cells would have nowhere to go accept the arterial wall where they will be unable to repair the infarcted tissue. In addition to these points, the cost of stents is very high as well. The entire procedure for fixing two vessels with a stent costs approximately $52,930.
IV.3.2.5   Polymer (Silk) Threads

A good-quality surgical thread has the following characteristics:

- Is sufficiently strong and reasonably thick
- Will easily pass through tissue, will not be hung up on tissue particles
- Flexible, easy to knot without unraveling the thread
- Will not fray

Synthetic threads can be broken into two main groups: nonabsorbable sutures and absorbable sutures. Nonabsorbable sutures were the most common types of threads used in surgery until the recent developments with biodegradable synthetics and are still used on topical wounds. The most prominent nonabsorbable suture is silk thread. 25ft of 0.08mm thick silk surgical thread runs at $35.80 per roll. There are various absorbable sutures available on the market currently, the most common include: polyglycolic acid sutures, polyglactin 910 sutures, chromic catgut sutures, plain catgut sutures, polydioxanone sutures and poliglecaprone 25 sutures. Exact prices for the absorbable threads are unknown since many are new to the market.

Synthetic threads have been used for many years to effectively sew tissue together. The biodegradable threads offer an additional benefit that as the wound heals; the suture will dissolve over time eliminating the need to remove the threads. However, even with biodegradable threads, synthetic threads are not the ideal material to place in the body. Any foreign object placed in the body can induce an immunoresponse and will not necessarily aid in the healing process. Another key point is that the surgical threads can not necessarily be seeded with cells. The synthetic materials from which the synthetic
threads are constructed are not capable of sustaining cell life and may be cytotoxic to the cells.

Researchers at University College London in the United Kingdom have created “microthreads from polymers containing living cells, using a technique called electrospinning. These biologically active threads could be formed into medical scaffolds, to deliver cells directly to tissue and promote healing.” The United Kingdom researchers utilize synthetic materials and electrospinning to create a different type of “thread.” The actual product of electrospinning is a very fine network of nets and webs that have no order or organization. Along with synthetic materials, therapeutic cells have been introduced into the mixture as well, creating a spun network of webbing and cells. This network of nets and webbing is approximately 1000 times smaller than that of the WPI Microthread technology, making it near impossible to utilize as a surgical thread (invisible to the naked eye). This small diameter also violates the first principle of a good-quality thread, which requires a thread to be reasonably strong and thick.

IV.3.2.6  Current Medicinal Treatments

The purpose of medication is to make the patient feel better in the short and long run. Heart medications are used to help patients live longer, have fewer symptoms, ease breathing, increase activity levels, reduce swelling and keep them out of the hospital. To control the various symptoms that occur after a heart attack, most patients will be prescribed several different heart medications. While there are a variety of heart medications, the most common types of heart medications are: ACE (angiotensin-converting enzyme) inhibitors, beta-blockers, digoxin, diuretics, aldosterone antagonists, and isosorbide dinitrate/hydralazine.
Angiotensin-Converting Enzyme (ACE) Inhibitors

ACE Inhibitors treat high blood pressure by blocking an enzyme that leads to the release of a substance called angiotensin (which causes blood vessels to constrict). ACEIs relax blood vessels throughout the body which lowers blood pressure, thereby reducing strain on the heart\textsuperscript{56,57}. In 2004, ACEIs were the third most widely prescribed class of medicines for heart failure. There is a substitute for ACEIs known as an angiotensin receptor blocker (ARBs) for patients who react adversely to ACEIs\textsuperscript{58}. The benefits and side effects are the same; ARBs block angiotensin in a different manner. Side effects of ACEIs and ARBs include: lose of potassium, dizziness, fever and chills, hoarse throat, swelling in extremities, trouble swallowing or breathing, abdominal or chest pain, jaundice, skin rash, joint pain, light-headedness, fainting, nausea, vomiting, numbness, confusion, persistent dry cough, fatigue and headaches\textsuperscript{57}.

Beta-blockers

Beta-blockers treat high-blood pressure by blocking adrenaline. Adrenaline increases heart rate, causing the heart muscle to contract more strongly, and constricts arteries throughout; which causes blood pressure to rise\textsuperscript{56}. By blocking adrenaline, the beta-blockers decrease the heart rate and reduce the strain put on the muscle, thereby decreasing blood pressure. It has been found that if a patient takes a beta-blocker after a heart attack, their risk of a repeated attack and death is lowered by 15% to 25\%\textsuperscript{59}. Beta-blockers have become a standard of medicinal therapy for infarction patients. Side effects include: decreased blood circulation, sensitivity to sunlight, dizziness, light-headedness, fainting, fatigue,
weakness, depression, difficulty breathing, joint swelling, nausea, vomiting, anxiety, dry eyes, fever and numbness of skin\textsuperscript{56}.

\textit{Digoxin}

Digoxin, also known as digitalis, is a drug that is derived from the leaves of the foxglove plant. It improves heart function by correcting hormonal imbalances that worsens heart failure, strengthening the healthy tissue and the heart beats stronger and with a more regular rhythm. Since digoxin increases the strength of the heart beat, the flow of blood and oxygen throughout the patient’s heart is increased as well; making it easier for the patient to breathe and helping him/her to feel better\textsuperscript{59, 60}. Digoxin is one of the top prescribed medicines for patients who have suffered a heart attack since it improves the overall pumping capabilities of the damaged heart. Side effects of digoxin include: nausea or vomiting, blurred or colored vision, hallucinations, confusion, dizziness, rashes, enlarged breasts (men) or headaches\textsuperscript{56}.

\textit{Diuretics}

Diuretics help the body to rid itself of excess water and salt through urine. Releasing the excess fluid causes blood pressure to lower and the strain placed upon the heart to decrease. Diuretics also help alleviate pressure on the lungs and decreases swelling in a patient’s joints. Some diuretics can create potassium lose within the body, making it important to monitor a patient’s potassium levels while on this drug. Side effects include: dizziness, light-headedness, dryness of mouth, irregular heartbeat, mood swings, nausea, vomiting, weakness, fatigue and weakened pulse\textsuperscript{56}. 
**Aldosterone Antagonist**

Aldosterone antagonists help to block the effects of the harmful stress hormone aldosterone. If the aldosterone hormonal level is elevated, it can result in high blood pressure as well as increased water and sodium retention in the body. Side effects include: breast enlargement or tenderness (particularly in men) and increased potassium levels\textsuperscript{56,58}.

**Isosorbide Dinitrate**

Isosorbide dinitrate relaxes the blood vessels, allowing them to widen and increases the blood flow. The increased blood flow reduces the amount of work on the heart, reducing the oxygen needs of the heart and minimizes chest pain. Side effects include: dizziness, light-headedness, headache, fainting, nausea, vomiting and irregular heartbeat\textsuperscript{56}.

**Hydralazine**

Hydralazine is used to treat patients with severe high blood pressure when it is urgent to lower blood pressure. This medication relaxes and dilates the blood vessels, allowing for a better blood flow. Side effects include: diarrhea, appetite loss, headache, nausea, vomiting, chest pain, difficulty breathing, fatigue, weakness, numbness, fever, chills and irregular heartbeat\textsuperscript{56}.

Medicinal treatments are effective at alleviating the symptoms after a heart attack. This method is non-invasive since medicine is taken orally. The cost of the medication can become rather expensive since most medications need to be taken for the rest of the patient’s life. However, the costs are heavily dependant on what types and combination
of drugs the physician prescribes. A drawback to this treatment is that it treats only the symptoms and it does not eliminate the cause.

IV.3.2.7 Microthreads versus the Competition

In order to compare and contrast Microthreads against the competition, a weighted matrix (Table 8) was developed by the author to rank important attributes of the various cardiac repair devices and procedures in an unbiased manner. The capabilities of each technology was written on a piece of paper and ranked without any association to the device it belonged to. The ratings were then collected and divided back into the technologies that they all belong to. Microthreads and competing technologies are compared based on a list of beneficial attributes provided in the first column. The matrix also provides the total attribute value scale and assigns a benefit value for each device based on research. The highest Total Values and Percentages indicate the “best” treatment based on available data.

<table>
<thead>
<tr>
<th>Potential</th>
<th>Total</th>
<th>Microthreads</th>
<th>Heart Patch</th>
<th>IV</th>
<th>Direct Injection</th>
<th>Medication</th>
<th>Stents</th>
<th>Polymer Threads</th>
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<td>5</td>
<td>4</td>
<td>1</td>
<td>4.5</td>
<td>4</td>
<td>5</td>
<td>4</td>
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<td>Biocompatibility</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>4</td>
<td>4</td>
<td>3</td>
<td>3</td>
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<tr>
<td>Cost</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td>4</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>3</td>
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<tr>
<td>Localized Delivery of Cells</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Repair Infarcted Tissue</td>
<td>5</td>
<td>4.5</td>
<td>4.5</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>1</td>
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<td>Minimal Side Effects</td>
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<td>1</td>
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<td>3</td>
<td>3</td>
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<td>Future Potential</td>
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<td>4</td>
<td>1</td>
<td>2</td>
<td>3</td>
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<tr>
<td>Clinical Trials</td>
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<td>4</td>
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<td># of Unknowns</td>
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<td>1</td>
<td>4</td>
<td>3</td>
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<td>Insurance Coverage</td>
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<td>Benefits to MI Patients</td>
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<td>5</td>
<td>4</td>
<td>2</td>
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<td>2</td>
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<tr>
<td>Low Chance of Immunoresponse</td>
<td>5</td>
<td>5</td>
<td>4</td>
<td>2</td>
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<td>Totals</td>
<td>61</td>
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<td>39.5</td>
<td>35.5</td>
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<td>35.5</td>
<td>32.5</td>
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<tr>
<td>Total Percentage</td>
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<td>65%</td>
<td>58%</td>
<td>56%</td>
<td>58%</td>
<td>53%</td>
<td>56%</td>
<td></td>
</tr>
</tbody>
</table>

Key

5 excellent
4 above average
3 average
2 fair
1 poor
0 N/A
Table 8 and Figure 19 indicate that Microthread technology is the most attractive choice for cardiac treatment. It was closely followed by the heart patch and the other five products fell into roughly the same categories. It should be noted, that current medicinal treatment still performed well enough to top three of the other competitors. This shows that medicine is still a strong competitor, despite the fact that it provides no appreciable benefit in the categories of repair of infarcted tissue and delivery of cell therapy.

Microthread technology has the ability to work with its competing technologies. Devices such as the HeartLander and the heart patch could benefit from a partnership with Microthreads. With the HeartLander, the Microthreads could be sutured directly into the infarcted tissue via the HeartLander’s needle channel (combining the strengths of the two technologies). The heart patch could benefit in an alternative way. Microthreads could be used to suture in the heart patch once the infarcted tissue is removed. This
would promote healing around the seam of the heart patch, making the patient healthier faster.

**IV.3.3 Marketing Microthread Technology**

**Patients’ Views:**

The patient’s views of Microthreads and their potential benefits are very important to the success of the technology. It will be essential to emphasize how a patient will benefit from the Microthread therapies and how it is different from other available treatments. Rehabilitation programs will be crucial in the patient’s return to full health after receiving Microthread treatments. However, rehabilitation is just as important for cardiac patients today. Yet it remains a very under-utilize resource. How will patients be motivated differently with the Microthreads? The answer is simple; Microthread therapies add a dimension of hope that is missing with current technology. Instead of learning how to function with a damaged heart, patients will be strengthening a heart with regenerated cells that closely match pre-infarction capability. This knowledge may motivate people to attend rehabilitation sessions.

Patients will still be prone to depression and other psychological post-myocardial infarction symptoms, but it is possible that the promise of improved heart function and vitality through the use of Microthread therapy can alleviate the severity of these emotions. The knowledge that the heart can be returned to a fully functional state without the need for an intensive surgery may ease patient anxiety and fear. Overall the stress upon patients, their families and loved ones will be greatly reduced because the procedure is minimally invasive; and not as intimidating as major surgery.
Advancement:

Microthreads technology must continue to be advanced from its current point. The inventor(s) should seek out and secure help and guidance from experts in the field of endoscopy (ensure the proper legal paperwork is in place to protect the proprietary nature of any research and inventions). These experts will aid with the development of a device specifically designed to locate and implant Microthreads in the heart muscle. This would ensure the threads to be delivered in the most effective manner, tailored to the threads’ specific requirements.

Microthreads currently have to be manufactured in a laboratory environment to strict standards including sterility. Because of the necessary manufacturing processes involved in creating threads, there is a heightened risk for contamination. Therefore, production must be improved and streamlined so that it can occur in a sterile environment. Once an appropriate Microthreads production methodology is developed, hospital staff, biomedical engineers and other health professionals must be trained in the methods. In the future, off-site (vendor based) bioreactors will allow for Microthreads to be manufactured in one centralized location and delivered directly to hospitals and other end users (i.e.: cardiologists, etc.).

IV.3.4 Licensing versus Starting a Business

Starting a business is an immense undertaking and has potential to be difficult for the co-inventors of this product at this time as they are all employed professors at Worcester Polytechnic Institute; though such a path is feasible if the creators so choose. Pursuing further development and funding for Microthread technology, as outlined earlier, would require significant effort. While they could choose to start one of the
following types of businesses: General Partnership, Limited Partnership, Limited Liability Partnership or a Limited Liability Corporation, it is this author’s opinion that none of those options are optimal for the development of their technology.

It is this author’s opinion that licensing the product information would be a more judicious approach to leveraging financial gain from this technology. A licensing is an agreement which allows a second party the use of intellectual property in the way that is stated in the licensing conditions, while leaving ownership of the intellectual property in the hands of the inventor(s). This would allow the professor(s) to further develop the product and bring useful technology to the market.

If the creators choose to go this route, it would be wise to inform the other professionals of this technology. An effective way to introduce Microthreads to medical professionals would be for the inventor(s) to prepare a series of informative articles that will be submitted to medical journals for publication (for example: Circulation, the American Heart Associations Journal). Since the President of the United States has signed has an executive order lifting the ban on federal funding for embryonic stem cell research, there are likely to be many researchers outside the scope of this project searching for ways to deliver these cells into the body. Microthread technology has potential to be the scaffold for other researchers to carry out their studies with the embryonic cells in addition to testing other cells that have been found to work similarly. This would allow the Microthread technology to be a lucrative vehicle for other researchers to accomplish their investigations.
IV.3.5 Health Insurance Coverage

IV.3.5.1 Health Insurance

Health insurance provides financial support for people affected by illness or injury. These policies typically cover doctor appointments, hospital visits to the emergency room, hospital stays, medicines, medical procedures as well as other medical expenses. Health insurance coverage comes in many forms, from the public health insurance of Medicare and Medicaid to group insurance provided by employers to private insurance to no insurance at all. Since there are a variety of insurance companies that handle health coverage, the policies of each institution offer differ wildly. Variables include medical conditions covered, the size of the deductible or co-payment (patient’s out-of-pocket expenses), the limits of coverage and the available treatment options.

IV.3.5.2 Health Insurance Reimbursement

To be ready to be marketed, a new medical device, pharmaceutical product or medical procedure, must qualify for health insurance reimbursement to be successful. A product or procedure that receives health insurance reimbursement has a proven track record for success. Reimbursement indicates that the insurance provider, allocating the funds, believes that the fee schedule is beneficial to all parties involved in the transaction. A fee schedule is the range of fees a doctor is allowed to charge for a procedure utilizing the medical protocols. Any type of life saving surgery qualifies for insurance reimbursement\(^6\).
IV.3.5.3 Qualifying for Health Insurance Reimbursement

In order to qualify for health insurance reimbursement, there are prerequisites that each product or procedure must fulfill. The first requirement is that the device or procedure must have FDA approval. Once this is obtained, devices (and not procedures) must then be reviewed for a reimbursement code by the Centers for Medicare and Medicaid Services (CMS). The reimbursement codes given by the CMS are part of the Healthcare Common Procedure Coding System (HCPCS). The HCPCS “was established in 1978 to provide a standardized coding system for describing the specific items and services provided in the delivery of health care. Such coding is necessary for Medicare, Medicaid, and other health insurance programs to ensure that insurance claims are processed in an orderly and consistent manner”\(^{(63)}\).

This system is divided into two subsystems known as Level I and Level II. Level I HCPCS’ are maintained by the American Medical Association and deal with medical procedures and services established by physicians and health care professionals. Level II HCPCS’ are completely under the CMS jurisdiction and identifies products, services and supplies that are not covered within the first level. Level II codes are then divided into National Permanent Level II HCPCS Codes and Temporary Level II HCPCS Codes. The National Permanent Level II HCPCS Codes “are for the use of all private and public health insurers. Since HCPCS is a national coding system all payers will be represented in the Workgroup including representatives from private insurance agencies, the Pricing, Data Analysis, and Coding (PDAC), and Medicaid will participate in the workgroup meetings and provide input as to what is necessary to meet each party’s program operating needs.”\(^{(64)}\). Permanent codes are updated once a year on January 1\(^{st}\). Temporary codes are used at the
discretion of the CMS for cases where a permanent code does not exist for a certain product or service. These products and services can be given a Temporary code which can be utilized by insurance companies until the product is eligible to be considered for permanent status at the end of the year. Currently 35% of all HCPCS codes are Temporary Level II.

A company or individual has the option to submit a code request to the CMS by using a standard format which includes:

- Cover letter outlining the code request and briefly summarizing why the code is needed.
- Completely answer all questions located within Alpha-Numeric HCPCS Coding Recommendation Format Information Supporting Coding Modification Recommendation (see Appendix VIII.17).
- FDA approval letter.
- Supporting documentation and/or descriptive material to further understanding of the medical benefits of the item.
- No more than three samples of the product, video tapes or compact discs.
- Sign and date every recommendation.

The entirety of the packet must be less than 40 pages in length and every question in the recommendation format must be completely answered (seen in Appendix VIII.17). For a more complete description of this portion of the process, refer to Appendix VIII.18.

It is important to note that these codes do not guarantee that a product or procedure will be covered by health insurance companies; they merely allow these devices or techniques to have the opportunity to be covered. Once FDA approval and a
HCPCS code have been obtained, the health insurance companies will take the device or
procedure into consideration. At that point the success of the device is based upon the
coverage of each specific health insurer, which devices the professionals choose to use, if
the device is effective and if it is more cost effective than other alternatives on the
market.

**IV.3.6 Food and Drug Administration (FDA) Regulations**

The FDA’s mandate is to protect the public’s health and well being. It is “the
authority” in determining whether or not products are safe and effective. The main role
of this organization as it pertains to the current point in the Microthreads life cycle is the
premarket approval process. The approval process is regulated by subgroups that address
specific areas within the healthcare spectrum. For Microthreads, jurisdiction will be
based on whether Microthreads are considered a medical device or a biological product.
There is no clear-cut method to determine which category this product will fall into based
upon the information that is made available by the FDA. However, there are regulations
for combination biologic devices similar to Microthreads. Under the Federal Food, Drug
and Cosmetic Act, Chapter 5, Subsection A, Section 503 (21 USC 353)(g)(1) it is stated
that the Secretary of the FDA will “assign an agency center to regulate products that
constitute a combination of a drug, device or biological product. The Secretary shall
determine the primary mode of action of the combination product”.

If the Secretary determines that Microthreads are a device, then the Center for
Devices and Radiological Health will perform the premarket review on the product;
whereas if it is ruled to be a biological product then it will be regulated by the Center for
Biologics Evaluation and Research. If Microthreads are ruled to be a biological product
rather than a device, they will have to go through extensive testing in order to be considered for approval.

In order to obtain approval, the researcher or organization must first inform the FDA of its intended product and the supposed effect of the product, the product must be tested in the laboratory and then tested in research animals\textsuperscript{68}. When the product is ready to begin the human testing phase, it must receive a special exemption from the FDA before the tests begin. The exemption is known as an investigational new drug application (IND)\textsuperscript{68}. In this application, the researcher or company must describe how they intend to perform the study, what the risks of the study are, and how the patients will be protected, and they need to provide data to support the validity of the study. In addition to this, the study needs the approval of a review board composed of scientific and medical advisors along with consumers. Researchers must also obtain the consent of patients participating in the study, and inform them of any risks and benefits that are associated with the treatment\textsuperscript{68}.
V Conclusion

Microthreads have a promising future in the cardiac market. With a potential market of 7.9 million patients, Microthreads offer unique advantages that no other product currently in the market or known-development is capable of. While there is competition for the cardiac niche aside from Microthreads, the advantages the threads hold are greater than the other products reviewed in this report. The novel idea of treating the cause rather than the effect of heart problems is uniquely captured by Microthreads. These “living threads” have the potential to regenerate infarcted heart tissue by anchoring cells directly to the injured tissue. In the future this technology will be implanted in tissue using minimally invasive procedures similar to cardiac catheterization, endoscopy or other specialized medical procedures. The biological nature of the threads, composed of naturally occurring proteins from the body as well as the subject’s own mesenchymal stem cells, will enhance the patients’ imunoresponse. If Microthreads can be manufactured and utilized for less than $363, in addition to receiving FDA approval and a HCPCS code, then they can be very successful in the cardiac market. It is this author’s opinion that Microthreads have the potential to greatly benefit cardiac patients and is a worthwhile venture to pursue.

Analysis has shown that, even with the limited scope of research completed to date, that Microthread technology has a promising future. The inventors of this technology should act quickly to seize upon the opportunities identified in this paper to promote the use of Microthread technology in research and in the medical industry. The inventors should develop a detailed action plan that includes: publishing informative articles in medical periodicals and research journals, a detailed development plan to
enhance the manufacture of Microthreads, contact teaching hospitals to determine and map out the most appropriate route to clinical trials and investigate potential vendors to help in the development of a Microthread delivery system that is minimally invasive.

It is critical that the inventors secure legal aid to ensure they are in a position to grant licensing rights of this technology to medical professionals, researchers and commercial vendors as opportunities present themselves. This more than anything may provide the fastest avenue to success for this new and exciting technology.

In conclusion, there is a market of at least 7.9 million patients that can benefit from the Microthread technology which offers unique advantages, such as treating the cause of the disease and the product’s autologous nature. If the Microthreads can be manufactured and utilized for less than $363, and receive FDA approval as well as a HCPCS code, then this technology will be successful on the cardiac market. Therefore it is this author’s opinion that Microthread technology is worth pursuing further.
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VII Glossary

1xDMEM *(1X DULBECCO’S MODIFICATION OF EAGLE’S MEDIUM)* – A concentrated solution of amino acids, vitamins and supplementary components (such as salts).

*Angiotensin-Converting Enzyme (ACE) Inhibitors* - Treat high blood pressure by blocking an enzyme that leads to the release of a substance called angiotensin (which causes blood vessels to constrict). ACEIs relax blood vessels throughout the body which lowers blood pressure, thereby reducing strain on the heart.

*American Heart Association (AHA)* – National volunteer health agency dedicated to ending cardiovascular disease and stroke.

*Angiogenesis* – The growth of new blood vessels from pre-existing vessels.

*Beta-blockers* - Treats high-blood pressure by blocking adrenaline, which decreases the heart rate, reduces the strain put on the muscle, and decreases blood pressure.

*Cardiac Myocyte(s)* – Heart muscle cell(s).

*Cardiovascular Disease (CVD)* – Diseases that affect the heart or arteries.

*Collagen* – Long, strong, fibrous protein that provides an extracellular matrix for tissues and cells within the body.

*Cytotoxic* – Cell-killing, toxic to cells.

*Digoxin* – Improves heart function by correcting hormonal imbalances that worsens heart failure, strengthening the healthy tissue and the heart beats stronger and with a more regular rhythm

*Endocardium* – Layer of tissue that lines the inner chambers of the heart.

*Epicardium* – Outer layer of heart tissue, functions as a protective layer around the heart.

*Food and Drug Administration (FDA)* – Consumer protection agency focuses on monitoring products to protect the general public.

*Fibrin* – Fibrous protein, helps clot blood.

*Fibrinogen* – A soluble plasma glycoprotein.

*Healthcare Common Procedure Coding System (HCPCS)* – A standardized classification system used for claims processing.
**HEPES** – Organic chemical that adjusts the pH of a solution.

**Human Mesenchymal Stem Cells (hMSCs)** – These are cells that can differentiate into many cell types; these cells can be isolated from bone marrow.

**Immunoresponse** – When the immune system detects a foreign body and produces antibodies to attack it; whether or not it is beneficial to the patient.

**Infarct** – An area of tissue that is dead due to lack of blood and oxygen flow.

**Ischemia** – A restriction in blood supply that causes damage or death to tissue.

**Medicare** – A federal health care insurance program that provides coverage for people aged 65 years or older.

**Minimally Invasive** – A procedure that is less invasive than open surgery (where the surgeon opens the tissue to have direct access to the organs) but still accomplishes the same goal. This is not the same as non-invasive, which does not break the skin.

**Myocardial Infarction** – A heart attack; death of cardiac tissue

**Myocardium** – The heart’s muscular wall (the middle layer in the heart), contracts causing heart to pump.

**Necrosis** – Death of cells or living tissue.

**Neurons** – Responsive cells in the nervous system that transmit information through electrochemical signaling.

**Oligodendrocytes** – Insulate axons in the central nervous system.

**Platform Technology** – A technology that can be applied in multiple fields, rather than just one.

**Scaffold** – A temporary framework that provides support.

**Suture** – Thread structures that sewn through portions of the human body together after they have been severed from injury, surgery or incisions to hold the flaps together and allow for healing.

**Thrombin** – A protein that converts fibrinogen to fibrin.

**Vascular** – Relating to the blood vessels of the body.
VIII Appendices

VIII.1 Interview with Professor Gaudette

Inquire about RNIH, CUTTOR, MTTC feedback
He provided hard copies of the responses, which are located in the MQP binder.

What are the advantages/benefits of the Microthreads?
Microthreads deliver cells directly into the inner heart wall, where the infarcted tissue causes the greatest damage and problems. The threads accomplish this in a much more direct way than any other device in trials thus far. Injection techniques just have the cells pumped out of the heart as soon as the needle is pulled out. Balloon stents allow for enough time for a few cells to attach before it is pulled out and the cells float away. The IV application of cells does not allow for many cells to make it to the heart let alone attach to the inner heart wall (and there is the additional risk that the heart cells will attach to the lungs!). The other prominent technique is a heart patch that is highly invasive and does not leave much room for error. It requires removing the dead portion of the heart, and sewing new, healthy tissue into the gap. While this gets rid the damaged tissue, the perimeter of the patch will be highly subject to potentially breaking off due to the strain and stresses the heart would put on the sutures.

Can Microthreads be sutured into the heart in a minimally invasive way?
Right now, no. But they could be used that way in the future, through the use of cardiac endoscopes. This procedure would be performed by a cardiologist, and not a surgeon. Surgeons are in charge of the highly invasive tasks.

-Side note: Learned that there is strong competition between cardiologists and surgeons, they try to keep their customers unless they absolutely have to send them so someone else. Cardiologists are the ones that refer patients to the surgeons.

Do/will the cells sheer off when passed through the heart tissue?
This is testing that they still need to do. They were hoping to use some of the grant money to further research this portion, however, there are some theories and ideas that they already have regarding the sheering of the seeded cells. It is believed that the cells will in fact shear off when passed through the tissue of the heart. In order to preempt this, they are planning on creating protective sheaths that will cover the threads that will prevent the cells from sheering off. This sheath will allow O$_2$ to pass through so that the cells will stay alive, but will not allow the cells to pass through the wall. This sheath will then be pulled out once the threads have been sutured into the heart wall.

Are the strings strong enough to withstand the contractions of the heart?
Yes, they are strong enough. As a matter of fact, they also allow for a little bit of give, so it can beat with the heart.
Will they damage the heart if sutured in too tightly? By constricting the muscle movement?
Movement is constricted by scar tissue that forms around the punctures created by sutures. It is unknown as of now whether the Microthreads will create this type of scarring or not. This is something that further studies are needed for.

Are Microthreads able to repair small amounts of dead tissue, or large amounts?
As of now, this is not known. Further research is required in this area.

Additional Information Given About Microthreads:
- Bundled together in groups of 10, and then looped through a needle (so that the threads are basically a bundle of 20).
- After about 3 days, the maximum amount of cells present on the threads, any longer and they run out of room to grow and begin to die.
VIII.2 Questions Answered by Professor Marsha Rolle

What is the approximate amount of money that has gone into developing Microthreads? (**In order to determine how much development-expenses will factor into the potential pricing of the device)

GP

How can the Microthreads be manufactured on a larger scale? How many can be made at one time?

GP

If clinical trials were to occur, would the Microthreads have to be manufactured on location?

No – I think it would be too difficult/not feasible. I envision manufacturing these in a GLP/GMP facility and spending the time/money/effort to design systems for packaging and transporting them. We have started doing this on a small scale for research purposes with a collaborator in New York. However, cell-seeding (i.e., with the patient’s own cells) may be performed on site (this is what our collaborator is doing).

If yes to previous question, what type of training would people have to undergo to be able to manufacture the threads correctly? Or would it have to be accomplished close to WPI so that the Microthreads could be manufactured correctly?

See above.

What is the current shelf-life of a Microthread?

Not known exactly, and will probably depend on whether cells and serum are present. The half life of a dry thread is much longer than a hydrated thread, and cell-seeded threads only last for days. Again, I think that making, sterilizing and shipping dehydrated threads may be more feasible than hydrated, cell-loaded threads. Hydrated, cell-seeded threads will probably need to be made, packaged, shipped overnight and used within a day or two.

What time frame does a Microthread have to be used at its optimal point of life (when it would be the most effective)?

See above.
How long does it take to make a Microthread currently?
GP.

How long would it take to create a Microthread with the patient’s own adult mesenchymal stem cells upon the surface?
Again, for this application, I imagine dry threads may be hydrated and seeded on site.

What kind of precautions have to be taken to create a Microthread?
GP.

How sterile must the environment be? What is the likelihood of contamination?
Threads can be sterilized after the process, but ideally, the process should be done aseptically.

How old does the infarct need to be before the sutures can be put into place? Does the infarct have to be scarred over or can it be sutured in while the heart tissue is still dying? What does the timeline for infarct-repair look like?
Scar will probably be harder to suture into than provisional matrix/early wound healing tissue/acute infarct. The time course of infarct “healing” in humans takes several months – the acute phase occurs in the first few weeks.

Is there a size limitation as to the how large of an infarct the Microthreads will repair?
There may be a point where it is no longer feasible (cost of microthreads needed is too high to justify). Also, if too many microthreads are sutured into the heart, it may compromise the strength of the tissue.

Does the scar tissue have to be removed before the Microthread sutures are sewn into the heart wall?
No – our ideal application would be to suture without surgical resection of the scar. This would be less “invasive”.

Where will the Collagen and/or Fibrin that the threads will be made of come from?
GP. I think we discussed this – ideally from human sources, although bovine products are approved by the FDA.

**If it is not autologous, will there be an immuno-response in the patient?**

GP. Again, bovine materials are approved for use in human patients.

**How are the threads sterilized? How will the threads remain sterilized?**

Right now, alcohol is used for our “bench top” sterilization procedures. We have not experimented with packaging or other methods, so we don’t know how they will affect thread stability. Ethylene oxide gas may be an option if there are no cells on the threads.

**Any information on the pricing of some of the competitors.**

Don’t know.

**Microthreads vs. the Heart Patch: first hand opinion on both.**

- **pricing for Heart Patch?**

  ??? As we discussed, a potential advantage of a thread over a patch is that the patch is epicardial, but the threads can be placed anywhere within the heart wall.
VIII.3 Questions: Professors Pins & Gaudette in Collaboration
(sent in conjunction with individual answers)

What is the approximate amount of money that has gone into developing Microthreads? (**In order to determine how much development-expenses will factor into the potential pricing of the device**)
To date, we have spent $23,400 (in the form of a grant) on the development of these threads. We anticipate receiving a second grant for $405,000 that we allow us to scale up and validate these threads in an animal model.

How can the Microthreads be manufactured on a larger scale? How many can be made at one time?

Unfortunately, I do not have a good answer for this at present.

If clinical trials were to occur, would the Microthreads have to be manufactured on location?

NO

What is the current shelf-life of a Microthread?

We have not analyzed this, but I think that 14-28 days is a reasonable estimate.

What time frame does a Microthread have to be used at its optimal point of life (when it would be the most effective)?

Again, we have not analyzed this. I would presume that their properties remain constant for 14-28 days.

How long does it take to make a Microthread currently?

Fibrin microthreads take approximately 24 hours to make.
Collagen threads take approximately 3 days to make.

How long would it take to create a Microthread with the patient’s own adult mesenchymal stem cells upon the surface?

Threads can be ready at anytime, but it takes weeks to grow up stem cells once they have been isolated.
What kind of precautions have to be taken to create a Microthread?

The starting material must come from a controlled, screened (virus-free, pathogen-free) and reproducible animal source.

How sterile must the environment be? What is the likelihood of contamination?

Must be sterile. There can be no likelihood of contamination.

How old does the infarct need to be before the sutures can be put into place? Does the infarct have to be scarred over or can it be sutured in while the heart tissue is still dying? What does the timeline for infarct-repair look like?

This is currently unknown.

Is there a size limitation as to the how large of an infarct the Microthreads will repair?

Not currently known.

Does the scar tissue have to be removed before the Microthread sutures are sewn into the heart wall?

Hopefully not.

Where will the Collagen and/or Fibrin that the threads will be made of come from?

I anticipate that the collagen and the fibrin will come from either a bovine or a human source.

If it is not autologous, will there be an immuno-response in the patient?

Depends on the stem cells that are being delivered.

How are the threads sterilized? How will the threads remain sterilized?

At present, threads are ethanol or isopropanol sterilized. The remain sterile be being handled using strictly sterile protocols after sterilization.

Any information on the pricing of some of the competitors.

No none competitors.
Microthreads vs. the Heart Patch: first hand opinion on both.

- Pricing for Heart Patch?

Depending on size of patch, ~$500-1,000 for heart patch without cells.
**VIII.4 Questions: Professor Glenn Gaudette January 21, 2009**

If clinical trials were to occur, would the Microthreads have to be manufactured on location?

**NO**

How sterile must the environment be? What is the likelihood of contamination?

Must be sterile. There can be no likelihood of contamination.

How old does the infarct need to be before the sutures can be put into place? Does the infarct have to be scarred over or can it be sutured in while the heart tissue is still dying? What does the timeline for infarct-repair look like?

This is currently unknown.

Is there a size limitation as to the how large of an infarct the Microthreads will repair?

Not currently known.

Does the scar tissue have to be removed before the Microthread sutures are sewn into the heart wall?

Hopefully not.

If it is not autologous, will there be an immuno-response in the patient?

Depends on the stem cells that are being delivered.

Any information on the pricing of some of the competitors.

No none competitors.

**Microthreads vs. the Heart Patch: first hand opinion on both.**

- pricing for Heart Patch?

Depending on size of patch, ~$500-1,000 for heart patch without cells.
VIII.5 E-mail Correspondence with Pharmacist Matthew Moen

Lanoxin is the brand name for digoxin, digitek is a branded generic. Cardoxin is not a name I'm familiar with, it appears dipyridamole is marketed under this brand name in Israel (totally different drug than digoxin). Digoxin is available in 0.125mg and 0.25mg tablets. #30 0.125mg tablets = $15.13

These are 3 different formulations of isosorbide dinitrate (available as a generic). Isosorbide dinitrate is available in 5, 10, 20, and 40mg tablets, typically dosed 2 to 3 times daily. #30 20mg tablets = $17.07

Apresoline is a brand name for hydralazine (available as a generic). It is available in 10, 25, 50, and 100mg tablets. Dosing can vary significantly depending upon the condition being treated but the maximum is typically 300mg per day delivered in divided doses. #30 of the 50mg tablets = $26.90

Apresazide is a combination of hydralazine & hydrochlorothiazide. Unfortunately it's not stocked by our wholesaler so I can't offer any pricing.

BiDil is a combination of isosorbide dinitrate and hydralazine, available in a 20mg-37.5mg tablet. Typical dosing is 1 tablet 3 times daily. Cost for #30 tablets = $77.50

Bumetanide is available in 0.5mg, 1mg, and 2mg tablets, typically dosed once daily. #30 1mg tablets = $23.36

Chlorothiazide is available in 250mg and 500mg tablets. Typical dosing is 500 to 1000mg once to twice daily. #30 500mg tablets = $17.95

Hydrochlorothiazide is available in 12.5mg, 25mg, and 50mg formulations, typically dosed once daily. #30 25mg tablets = $12.38

Spironolactone is available in 25, 50, and 100mg tablets, typically dosed once daily. #30 50mg tablets = $34.47

Eplerenone is available in 25 and 50mg tablets, typically dosed once daily. #30 25mg tablets = $133.07

Let me know if there's any other information you require.

Matt
## VIII.6 ACEI Cost Table

<table>
<thead>
<tr>
<th>Generic Name and Dose</th>
<th>Brand Name</th>
<th>Frequency of Use (per day)</th>
<th>Average Monthly Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Captopril 12.5 mg Capoten</td>
<td>three</td>
<td>$133</td>
<td></td>
</tr>
<tr>
<td>Captopril 12.5 mg Generic</td>
<td>three</td>
<td>$30</td>
<td></td>
</tr>
<tr>
<td>Captopril 25 mg Capoten</td>
<td>three</td>
<td>$131</td>
<td></td>
</tr>
<tr>
<td>Captopril 25 mg Generic</td>
<td>three</td>
<td>$31</td>
<td></td>
</tr>
<tr>
<td>Captopril 50 mg Capoten</td>
<td>three</td>
<td>$220</td>
<td></td>
</tr>
<tr>
<td>Captopril 50 mg Generic</td>
<td>three</td>
<td>$44</td>
<td></td>
</tr>
<tr>
<td>Captopril 100 mg Capoten</td>
<td>three</td>
<td>$271</td>
<td></td>
</tr>
<tr>
<td>Captopril 100 mg Generic</td>
<td>three</td>
<td>$55</td>
<td></td>
</tr>
<tr>
<td>Lisinopril 10 mg Prinivil</td>
<td>one</td>
<td>$38</td>
<td></td>
</tr>
<tr>
<td>Lisinopril 10 mg Zestril</td>
<td>one</td>
<td>$40</td>
<td></td>
</tr>
<tr>
<td>Lisinopril 10 mg Generic</td>
<td>one</td>
<td>$18</td>
<td></td>
</tr>
<tr>
<td>Lisinopril 20 mg Prinivil</td>
<td>one</td>
<td>$41</td>
<td></td>
</tr>
<tr>
<td>Lisinopril 20 mg Zestril</td>
<td>one</td>
<td>$44</td>
<td></td>
</tr>
<tr>
<td>Lisinopril 20 mg Generic</td>
<td>one</td>
<td>$20</td>
<td></td>
</tr>
<tr>
<td>Lisinopril 30 mg Zestril</td>
<td>one</td>
<td>$59</td>
<td></td>
</tr>
<tr>
<td>Lisinopril 30 mg Generic</td>
<td>one</td>
<td>$26</td>
<td></td>
</tr>
<tr>
<td>Lisinopril 40 mg Prinivil</td>
<td>one</td>
<td>$59</td>
<td></td>
</tr>
<tr>
<td>Lisinopril 40 mg Zestril</td>
<td>one</td>
<td>$61</td>
<td></td>
</tr>
<tr>
<td>Lisinopril 40 mg Generic</td>
<td>one</td>
<td>$27</td>
<td></td>
</tr>
<tr>
<td>Ramipril 1.25 mg Altace</td>
<td>one</td>
<td>$44</td>
<td></td>
</tr>
<tr>
<td>Ramipril 2.5 mg Altace</td>
<td>one</td>
<td>$50</td>
<td></td>
</tr>
<tr>
<td>Ramipril 5 mg Altace</td>
<td>one</td>
<td>$54</td>
<td></td>
</tr>
<tr>
<td>Ramipril 10 mg Altace</td>
<td>one</td>
<td>$65</td>
<td></td>
</tr>
<tr>
<td>Trandolapril 1 mg Mavik</td>
<td>one</td>
<td>$41</td>
<td></td>
</tr>
<tr>
<td>Trandolapril 2 mg Mavik</td>
<td>one</td>
<td>$42</td>
<td></td>
</tr>
<tr>
<td>Trandolapril 4 mg Mavik</td>
<td>one</td>
<td>$41</td>
<td></td>
</tr>
</tbody>
</table>
### VIII.7 Beta-Blocker Cost Table

<table>
<thead>
<tr>
<th>Generic Name and Dose</th>
<th>Brand Name</th>
<th>Frequency of Use</th>
<th>Average Monthly Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atenolol 25 mg</td>
<td>Tenormin</td>
<td>One a day</td>
<td>$47</td>
</tr>
<tr>
<td>Atenolol 25 mg</td>
<td>Generic</td>
<td>One a day</td>
<td>$10</td>
</tr>
<tr>
<td>Atenolol 50 mg</td>
<td>Tenormin</td>
<td>One a day</td>
<td>$47</td>
</tr>
<tr>
<td>Atenolol 50 mg</td>
<td>Generic</td>
<td>One a day</td>
<td>$10</td>
</tr>
<tr>
<td>Atenolol 100 mg</td>
<td>Tenormin</td>
<td>One a day</td>
<td>$71</td>
</tr>
<tr>
<td>Atenolol 100 mg</td>
<td>Generic</td>
<td>One a day</td>
<td>$13</td>
</tr>
<tr>
<td>Carvedilol 6.25 mg</td>
<td>Coreg</td>
<td>Two a day</td>
<td>$124</td>
</tr>
<tr>
<td>Carvedilol 12.5 mg</td>
<td>Coreg</td>
<td>Two a day</td>
<td>$124</td>
</tr>
<tr>
<td>Carvedilol 25 mg</td>
<td>Coreg</td>
<td>Two a day</td>
<td>$122</td>
</tr>
<tr>
<td>Metoprolol tartrate 50 mg</td>
<td>Lopressor</td>
<td>One a day</td>
<td>$35</td>
</tr>
<tr>
<td>Metoprolol tartrate 50 mg</td>
<td>Generic</td>
<td>One a day</td>
<td>$9</td>
</tr>
<tr>
<td>Metoprolol tartrate 100 mg</td>
<td>Lopressor</td>
<td>One a day</td>
<td>$52</td>
</tr>
<tr>
<td>Metoprolol tartrate 100 mg</td>
<td>Generic</td>
<td>One a day</td>
<td>$12</td>
</tr>
<tr>
<td>Propranolol 10 mg</td>
<td>Inderal</td>
<td>Two a day</td>
<td>$33</td>
</tr>
<tr>
<td>Propranolol 10 mg</td>
<td>Generic</td>
<td>Two a day</td>
<td>$12</td>
</tr>
<tr>
<td>Propranolol 20 mg</td>
<td>Inderal</td>
<td>Two a day</td>
<td>$44</td>
</tr>
<tr>
<td>Propranolol 20 mg</td>
<td>Generic</td>
<td>Two a day</td>
<td>$13</td>
</tr>
<tr>
<td>Propranolol 40 mg</td>
<td>Inderal</td>
<td>Two a day</td>
<td>$56</td>
</tr>
<tr>
<td>Propranolol 40 mg</td>
<td>Generic</td>
<td>Two a day</td>
<td>$15</td>
</tr>
<tr>
<td>Propranolol 60 mg</td>
<td>Inderal</td>
<td>Two a day</td>
<td>$79</td>
</tr>
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<td>Propranolol 60 mg</td>
<td>Generic</td>
<td>Two a day</td>
<td>$22</td>
</tr>
<tr>
<td>Propranolol 80 mg</td>
<td>Inderal</td>
<td>Two a day</td>
<td>$87</td>
</tr>
<tr>
<td>Propranolol 80 mg</td>
<td>Generic</td>
<td>Two a day</td>
<td>$20</td>
</tr>
<tr>
<td>Propranolol (sustained release) 80 mg</td>
<td>Inderal</td>
<td>One a day</td>
<td>$52</td>
</tr>
<tr>
<td>Propranolol (sustained release) 80 mg</td>
<td>Generic</td>
<td>One a day</td>
<td>$36</td>
</tr>
<tr>
<td>Propranolol (sustained release) 120 mg</td>
<td>Inderal</td>
<td>One a day</td>
<td>$64</td>
</tr>
<tr>
<td>Propranolol (sustained release) 120 mg</td>
<td>Generic</td>
<td>One a day</td>
<td>$40</td>
</tr>
<tr>
<td>Timolol 10 mg</td>
<td>Blocadren</td>
<td>Two a day</td>
<td>$69</td>
</tr>
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<td>Timolol 10 mg</td>
<td>Generic</td>
<td>Two a day</td>
<td>$25</td>
</tr>
<tr>
<td>Timolol 20 mg</td>
<td>Blocadren</td>
<td>Two a day</td>
<td>$72</td>
</tr>
<tr>
<td>Timolol 20 mg</td>
<td>Generic</td>
<td>Two a day</td>
<td>$45</td>
</tr>
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</table>
### VIII.8 Digoxin, Diuretics and Aldosterone Cost Tables

#### Digoxin Cost Comparison Table

<table>
<thead>
<tr>
<th>Generic Name and Dose</th>
<th>Brand Name</th>
<th>Frequency of Use (per day)</th>
<th>Average Monthly Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digoxin 0.125mg</td>
<td>Digoxin</td>
<td>1</td>
<td>$15.13</td>
</tr>
<tr>
<td>Digoxin 0.25mg</td>
<td>Digoxin</td>
<td>1</td>
<td>$20.70</td>
</tr>
</tbody>
</table>

#### Diuretics Cost Comparison Table

<table>
<thead>
<tr>
<th>Generic Name and Dose</th>
<th>Brand Name</th>
<th>Frequency of Use (per day)</th>
<th>Average Monthly Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bumetanide 0.5mg</td>
<td></td>
<td>1</td>
<td>$23.36</td>
</tr>
<tr>
<td>Bumetanide 1mg</td>
<td></td>
<td>1</td>
<td>$23.36</td>
</tr>
<tr>
<td>Bumetanide 2mg</td>
<td></td>
<td>1</td>
<td>$23.36</td>
</tr>
<tr>
<td>Chlorothiazide 250mg</td>
<td></td>
<td>500mg - 1000mg, 1 to 2</td>
<td>$17.95 - $35.90</td>
</tr>
<tr>
<td>Chlorothiazide 500mg</td>
<td></td>
<td>500mg - 1000mg, 1 to 2</td>
<td>$17.95 - $35.90</td>
</tr>
<tr>
<td>Hydrochlorothiazide 12.5mg</td>
<td></td>
<td>1</td>
<td>$12.38</td>
</tr>
<tr>
<td>Hydrochlorothiazide 25mg</td>
<td></td>
<td>1</td>
<td>$12.38</td>
</tr>
<tr>
<td>Hydrochlorothiazide 50mg</td>
<td></td>
<td>1</td>
<td>$12.38</td>
</tr>
</tbody>
</table>

#### Aldosterone Antagonists Cost Comparison Table

<table>
<thead>
<tr>
<th>Generic Name and Dose</th>
<th>Brand Name</th>
<th>Frequency of Use (per day)</th>
<th>Average Monthly Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spironolactone 25mg</td>
<td></td>
<td>1</td>
<td>$34.47</td>
</tr>
<tr>
<td>Spironolactone 50mg</td>
<td></td>
<td>1</td>
<td>$34.47</td>
</tr>
<tr>
<td>Spironolactone 100mg</td>
<td></td>
<td>1</td>
<td>$34.47</td>
</tr>
<tr>
<td>Epleremone 25mg</td>
<td></td>
<td>1</td>
<td>$133.07</td>
</tr>
<tr>
<td>Epleremone 50mg</td>
<td></td>
<td>1</td>
<td>$133.07</td>
</tr>
</tbody>
</table>
### VIII.9 Isosorbide, Hydralazine and Combination Cost Table

#### Isosorbide Dinitrate Cost Comparison Table

<table>
<thead>
<tr>
<th>Generic Name and Dose</th>
<th>Brand Name</th>
<th>Frequency of Use (per day)</th>
<th>Average Monthly Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isosorbide Dinitrate 5mg</td>
<td>Isosorbide Dinitrate</td>
<td>2 to 3</td>
<td></td>
</tr>
<tr>
<td>Isosorbide Dinitrate 10mg</td>
<td>Isosorbide Dinitrate</td>
<td>2 to 3</td>
<td></td>
</tr>
<tr>
<td>Isosorbide Dinitrate 20mg</td>
<td>Isosorbide Dinitrate</td>
<td>2 to 3</td>
<td>$34.14 to $51.21</td>
</tr>
<tr>
<td>Isosorbide Dinitrate 40mg</td>
<td>Isosorbide Dinitrate</td>
<td>2 to 3</td>
<td></td>
</tr>
</tbody>
</table>

#### Hydralazine Cost Comparison Table

<table>
<thead>
<tr>
<th>Generic Name and Dose</th>
<th>Brand Name</th>
<th>Frequency of Use (per day)</th>
<th>Average Monthly Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydralazine 10mg</td>
<td>Apresoline</td>
<td>300mg/day</td>
<td></td>
</tr>
<tr>
<td>Hydralazine 25mg</td>
<td>Apresoline</td>
<td>300mg/day</td>
<td></td>
</tr>
<tr>
<td>Hydralazine 50mg</td>
<td>Apresoline</td>
<td>300mg/day</td>
<td>$4,842.00</td>
</tr>
<tr>
<td>Hydralazine 100mg</td>
<td>Apresoline</td>
<td>300mg/day</td>
<td></td>
</tr>
</tbody>
</table>

#### I.D. & Hydralazine Cost Comparison Table

<table>
<thead>
<tr>
<th>Generic Name and Dose</th>
<th>Brand Name</th>
<th>Frequency of Use (per day)</th>
<th>Average Monthly Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>BiDil 20mg - 37.5mg</td>
<td></td>
<td>1</td>
<td>$77.50</td>
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</table>
### VIII.10 Medication Yearly Costs: Minimum, Mean, Maximum

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Minimum</th>
<th>Mean</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACEI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lisinopril 10 mg</td>
<td>$18.00</td>
<td>$216.00</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Captopril 100 mg</td>
<td>$271.00</td>
<td>$3,252.00</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ramipril 10 mg</td>
<td>$65.00</td>
<td>$780.00</td>
<td></td>
</tr>
<tr>
<td><strong>BETA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Metoprolol tartrate 50 mg</td>
<td>$9.00</td>
<td>$108.00</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Carvedilol 12.5 mg</td>
<td>$124.00</td>
<td>$1,488.00</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Atenolol 50 mg</td>
<td>$47.00</td>
<td>$564.00</td>
<td></td>
</tr>
<tr>
<td><strong>Digoxin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Digoxin 0.125mg</td>
<td>$15.13</td>
<td>$181.56</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Digoxin 0.25mg</td>
<td>$20.70</td>
<td>$248.40</td>
<td></td>
</tr>
<tr>
<td><strong>Diuretics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bumetanide 1mg</td>
<td>$23.36</td>
<td>$280.32</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chlorothiazide 500mg</td>
<td>$17.95</td>
<td>$215.40</td>
<td></td>
</tr>
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<td></td>
<td>Chlorothiazide 500mg</td>
<td>$35.90</td>
<td>$430.80</td>
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</tr>
<tr>
<td></td>
<td>Hydrochlorothiazide 25mg</td>
<td>$12.38</td>
<td>$148.56</td>
<td></td>
</tr>
<tr>
<td><strong>Aldosterone Antagonists</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Spironolactone 50mg</td>
<td>$34.47</td>
<td>$413.64</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Epleremone 25mg</td>
<td>$133.07</td>
<td>$1,596.84</td>
<td></td>
</tr>
<tr>
<td><strong>Isosorbide Dinitrate</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Isosorbide Dinitrate 20mg</td>
<td>$34.14</td>
<td>$409.68</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Isosorbide Dinitrate 20mg</td>
<td>$51.21</td>
<td>$614.52</td>
<td></td>
</tr>
<tr>
<td><strong>Hydralazine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hydralazine 50mg</td>
<td>$4,842.00</td>
<td>$58,104.00</td>
<td></td>
</tr>
<tr>
<td><strong>ID/H combo.</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>BiDil 20mg - 37.5mg</td>
<td>$77.50</td>
<td>$930.00</td>
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</table>
## VIII.11 Yearly Cost Matrix: Drug Treatment Combinations

<table>
<thead>
<tr>
<th>ACEI</th>
<th>BETA</th>
<th>Digoxin</th>
<th>Diuretics</th>
<th>Aldosterone Antagonists</th>
<th>Isosorbide Dinitrate</th>
<th>Hydralazine</th>
<th>ID/H combo.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Captopril 100 mg</strong></td>
<td>$3,252.00</td>
<td>$3,360.00</td>
<td>$3,888.00</td>
<td>$2,268.00</td>
<td>$1,344.00</td>
<td>$984.00</td>
<td>$58,104.00</td>
</tr>
<tr>
<td><strong>Rasipril 10 mg</strong></td>
<td>$3,252.00</td>
<td>$3,252.00</td>
<td>$3,888.00</td>
<td>$2,268.00</td>
<td>$1,344.00</td>
<td>$984.00</td>
<td>$58,104.00</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Digoxin</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>$181.56</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Diruetics</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bumetanide 1mg</strong></td>
</tr>
<tr>
<td><strong>Chlorothiazide 50mg</strong></td>
</tr>
<tr>
<td><strong>Chlorothiazide 50mg</strong></td>
</tr>
<tr>
<td><strong>Hydrochlorothiazide 25mg</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Aldosterone Antagonists</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Spironolactone 50mg</strong></td>
</tr>
<tr>
<td><strong>Epleremone 25mg</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Isosorbide Dinitrate</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Isosorbide Dinitrate 20mg</strong></td>
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<td><strong>Isosorbide Dinitrate 20mg</strong></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Hydralazine</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hydralazine 50mg</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>ID/H combo.</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BiDil 20mg - 37.5mg</strong></td>
</tr>
</tbody>
</table>
### VIII.12 Common Medication Combination Costs for Median Survival Years

<table>
<thead>
<tr>
<th>Medication Combinations</th>
<th>Cost per year</th>
<th>Median Survival Years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Digoxin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digoxin 0.125mg</td>
<td>$182</td>
<td>$1,344</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$1,888</td>
</tr>
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<td></td>
<td></td>
<td>$1,162</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>$363</strong></td>
</tr>
<tr>
<td>Digoxin 0.25mg</td>
<td>$248</td>
<td>$1,838</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$2,583</td>
</tr>
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<td></td>
<td></td>
<td>$1,590</td>
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<td></td>
<td></td>
<td><strong>$497</strong></td>
</tr>
<tr>
<td><strong>Digoxin + ACEI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digoxin 0.125mg +</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lisinopril 10 mg</td>
<td>$398</td>
<td>$2,942</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$4,135</td>
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<td></td>
<td></td>
<td>$2,544</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>$795</strong></td>
</tr>
<tr>
<td>Digoxin 0.125mg +</td>
<td>$3,434</td>
<td>$25,408</td>
</tr>
<tr>
<td>Captopril 100 mg</td>
<td></td>
<td>$35,709</td>
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<td>$21,975</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>$6,867</strong></td>
</tr>
<tr>
<td>Digoxin 0.125mg +</td>
<td>$962</td>
<td>$7,116</td>
</tr>
<tr>
<td>Ramipril 10 mg</td>
<td></td>
<td>$10,000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$6,154</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>$1,923</strong></td>
</tr>
<tr>
<td>Digoxin 0.25mg +</td>
<td>$464</td>
<td>$3,437</td>
</tr>
<tr>
<td>Lisinopril 10 mg</td>
<td></td>
<td>$4,830</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$2,972</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>$929</strong></td>
</tr>
<tr>
<td>Digoxin 0.25mg +</td>
<td>$3,500</td>
<td>$25,903</td>
</tr>
<tr>
<td>Captopril 100 mg</td>
<td></td>
<td>$36,404</td>
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<td></td>
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<td>$22,403</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>$7,001</strong></td>
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<tr>
<td>Digoxin 0.25mg +</td>
<td>$1,028</td>
<td>$7,610</td>
</tr>
<tr>
<td>Ramipril 10 mg</td>
<td></td>
<td>$10,695</td>
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<td>$6,582</td>
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<td><strong>$2,057</strong></td>
</tr>
<tr>
<td><strong>Digoxin + BETA</strong></td>
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</tr>
<tr>
<td>Digoxin 0.125mg +</td>
<td>$290</td>
<td>$2,143</td>
</tr>
<tr>
<td>Metoprolol tartrate 50 mg</td>
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<td>$3,011</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$1,853</td>
</tr>
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<td></td>
<td><strong>$579</strong></td>
</tr>
<tr>
<td>Digoxin 0.125mg +</td>
<td>$1,670</td>
<td>$12,355</td>
</tr>
<tr>
<td>Carvedilol 12.5 mg</td>
<td></td>
<td>$17,363</td>
</tr>
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<td></td>
<td></td>
<td>$10,685</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>$3,339</strong></td>
</tr>
<tr>
<td>Digoxin 0.125mg +</td>
<td>$746</td>
<td>$5,517</td>
</tr>
<tr>
<td>Atenolol 50 mg</td>
<td></td>
<td>$7,754</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$4,772</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>$1,491</strong></td>
</tr>
<tr>
<td>Digoxin 0.25mg + Metoprolol tartrate 50 mg</td>
<td>$356</td>
<td>$2,637</td>
</tr>
<tr>
<td>Digoxin 0.25mg +</td>
<td>$1,736</td>
<td>$12,849</td>
</tr>
<tr>
<td>Carvedilol 12.5 mg</td>
<td></td>
<td>$18,059</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$11,113</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>$3,473</strong></td>
</tr>
<tr>
<td>Digoxin 0.25mg +</td>
<td>$812</td>
<td>$6,012</td>
</tr>
<tr>
<td>Atenolol 50 mg</td>
<td></td>
<td>$8,449</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$5,199</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>$1,625</strong></td>
</tr>
</tbody>
</table>

† Median patient survival years for women 60-69yrs, men 70-79yrs
† Median patient survival years for women 70-79yrs
* Median patient survival years for women ≥ 80yrs
# Median patientsurvival years for men ≥ 80yrs
VIII.13 E-mail Correspondence for Collagen Pricing

We have received your product interest from Biocompare.

Attached for your review, please find a data sheet for our Human Collagen Type IV, Catalog #A33125H ($525.00/0.5mg) and Bovine Collagen Type III, Catalog #A33124B ($231.00/0.5mg).

Please note that United States customers may view pricing on-line after registering on our website.

Should you have any questions or need additional information, please do not hesitate to contact us or visit our website www.meridianlifescience.com.

Best Regards,

Anne Daley
Account Support Specialist

Meridian Life Science, Inc.

60 Industrial Park Road

Saco, ME 04072

Phone: 207-283-6500 Fax: 207-283-4800

e-mail: info@meridianlifescience.com

Website: www.meridianlifescience.com

Please note regarding pricing/specs:
Quote effective for 30 days
Price quoted in US dollars
Payment terms: With approved credit: net 30 days from invoice date. All others: Prepay
FOB Saco, ME, Freight PPD/ADD
Handling (one box) $25.00, additional box $15.00
Dry Ice charge: $20.00 if applicable
Price based upon full quantity in a single shipment.

Do you need a HAMA Blocker manufactured to your specifications? Contact us via http://meridianlifescience.com/products/hama.asp

A ISO 9001:2000 Certified company
VIII.14 SPECIFICATION SHEET: Collagen Type IV

Important Note: Centrifuge before opening to ensure complete recovery of vial contents.

Catalog #: A33125H          Lot #: 1L34408

Description: Human Collagen Type IV

Source: Placental villi

Format: Purified, Liquid

Purification: >90% pure (SDS-PAGE)
Controlled and limited pepsin digestion, followed by selective salt precipitation

Concentration: 0.5mg/ml (dry weight)

Buffer: 500mM Acetic acid

Preservative: None

Application: Type IV collagen standard
Antigen for antibody production
Coating material for cell culture studies
Formation of collagen gels
Each laboratory should determine an optimum working titer for use in its particular application. Other applications have not been tested but use in such assays should not necessarily be excluded.

Storage: The collagen may be transferred into physiological buffers by dialysis at 2–8°C.
Purified collagen may be stored for several months at 2–8°C without appreciable loss of activity. For long term storage, aliquot and store at -20°C. Avoid multiple freeze/thaw cycles.

Inactivation: Pepsin digestion and storage in 500mM Acetic acid

Warnings: All materials should be handled as if potentially infectious. Generally accepted laboratory practices appropriate for infectious materials should be employed when handling this product.

References: The references listed below are for research purposes only.

1.0 FOR RESEARCH USE ONLY. NOT FOR USE IN DIAGNOSTIC PROCEDURES.

12/9/08
Important Note: Centrifuge before opening to ensure complete recovery of vial contents.

Catalog #: A33124B  Lot #: 13B03708

Description: Bovine Collagen Type III

Source: Placental villi

Format: Purified, Liquid

Purification: >90% (SDS-PAGE analysis). Controlled and limited pepsin digestion, followed by selective salt precipitation.

Concentration: 0.5mg/ml (determined by dry weight)

Buffer: 500mM acetic acid

Preservative: None

Applications: Type III collagen standard  
Antigen for antibody production  
Coating material for cell culture studies  
Formation of collagen gels  
To ensure lot-to-lot consistency, each lot of purified collagen is tested for conformance with characteristics of a standard reference reagent using SDS-PAGE analysis.

Storage: The collagen may be transferred into physiological buffers by dialysis at 2-8°C. Store at 2-8°C for several months without appreciable loss of activity. For long term storage, aliquot and store at –20°C. Avoid multiple freeze/thaw cycles.

Inactivation: Not applicable.

References: The references listed below are for research purposes only.  

1.1 FOR RESEARCH USE ONLY. NOT FOR USE IN DIAGNOSTIC PROCEDURES.

2/6/08
Executive Summary
- 1 paragraph explaining the product.
- 1 summary paragraph for each tab within the plan.
  - Segmenting with minor-headings to separate the paragraphs can be used.

Company Description
- **Company name:** Name of the Company
- **Form of Organization:** (Partnership, S Corporation, LLP, etc.)
- **Ownership:** Who owns the company? (ex. George Pins, etc.)
- **Location:** Where is the business located/headquartered?
- **Definition of the business:** What will the company be creating, why?
- **Company goals:** Overall goals of product in next 5-10 years.
- **Future Plans:** Development of business and product.

Milestones
- Income, development, insurance coverage, FDA approval, etc.

Marketing Tab – Most found in this Major Qualifying Project
- Overall Marketing Strategy
- Market Segmentation and Target Market
- Competition Analysis
- Intellectual Property Analysis
- Licensing

Sales and Distribution Tab
- Sales Process
- Key Players
- Distribution

Management Tab
- Management Team
- Company Structure
- Professionals

Operations Tab
- Operation Model and Procedures
- Manufacturing
- Vendors and Suppliers
- Business Location

Financial Tab
- Revenue
- Expenses
  - Cost to manufacture, packaging, shipping expenses, etc.
  - Salaries, R&D, administrative
- Five Year Financial Projection
  - Graph and table of data, as well as an explanation

Risks
*The potential risks and ways the risks can be mitigated.*
VIII.17   HCPCS Request Questionnaire

Alpha-Numeric HCPCS Coding Recommendation Format INFORMATION SUPPORTING CODING MODIFICATION RECOMMENDATION

1. For the purpose of publication on our request list and public meeting agenda on the HCPCS website, please provide a brief summary of your request (not to exceed 300 words). In this summary, please specify your request to modify the HCPCS code set: (e.g. number of new codes requested, recommended language; revise a code (provide old language and recommended language), discontinue a code). Include the name of the product, description, function, and the reason why existing codes do not adequately describe your product. For drugs, include the indications for use, action, dosage and route of administration, and how supplied. Text that exceeds the 300-word limit may be truncated and not appear on our published summary, therefore, it is important to provide a concise summary within the 300 word limit. CMS may edit your summary prior to publication.

2. Identify the Item (product or drug/biological) for which a Level II HCPCS Code is being requested.
   A) Trade or Brand Name:
   B) General Product Name or Generic Drug Name (active ingredient):
   C) FDA classification:
   D) Drug or Biological Y/N

3. Please check one HCPCS category from the following list, which most accurately describes the item identified in question #1:
   _ A) Medical/Surgical Supplies
   _ B) Dialysis Supplies and Equipment
   _ C) Ostomy/Urological Supplies
   _ D) Surgical Dressing
   _ E) Prosthetic
   _ F) Orthotic
   _ G) Enteral/Parenteral Nutrition
   _ H) Durable Medical Equipment
   _ I) Blood/Blood Products
   _ J) Drug/Biological
   _ K) Radiopharmaceutical
   _ L) Vision
   _ M) Hearing
   _ N) Other (please indicate/provide category)_________________________________

4. Is the item durable, if so, explain how it can withstand repeated use?
5. Describe the item fully in general terminology. What is it? What does it do? How is it used? Describe the patient population for whom the product is clinically indicated. Descriptive booklets, brochures, package inserts, as well as copies of published peer-reviewed articles on the item may be included in the information packet submitted for review, but they do not replace the requirement to fully respond to this question and fully describe the item.
For drugs and biologicals, include: A) indications for use, B) action, C) dosage and route of administration, D) package insert and, E) how supplied.

6. Describe how the item/product is primarily and customarily used to serve a medical purpose.
7A) Identify similar products and their manufacturers.
(If a drug - list other drugs by trade name marketed under the same active ingredient category/generic name.)
7B) Identify significant differences between this item and other products listed above.
(Include differences in item cost; material; product design; how it is used; different mechanism of operation, differences in function/treatment provided to a patient; clinical indication; and clinical outcome.)
7C) Complete item 7C only if you are making a claim of significant therapeutic distinction).
Claims of significant therapeutic distinction when compared to the use of other, similar items, must be described in detail. Articulate the clinical theory behind the claim, including differences in the product or its operation as it compares to currently coded products. Specify how the product results in a significantly improved medical outcome or significantly superior clinical outcome. (Please refer to the HCPCS decision tree for additional information.) Provide the best available information related to your claim. Include copies of all articles that result from your systematic analysis of the available literature. Information submitted should be as complete as possible. Unfavorable articles should be provided with any appropriate rebuttal or explanation. If the articles submitted cause you to exceed the overall 40-page limit, then submit one reference copy of each article and 35 copies of the application.

8. Answer each of the questions A), B), and C) below:
A) List any 3rd party payers that pay for this product
B) List any codes that are currently being billed to those payers for this product.
C) Explain why existing code categories are inadequate to describe the item.

9.
A) Is this product prescribed by a health care professional?
B) If yes - who prescribes the product and in what setting(s) is the product prescribed?

10.
A) Is the item useful in the absence of an illness or injury?
B) Explain:
11. Provide the date that the item/product was approved for marketing by the FDA. Attach copy of the FDA approval letter including the 510K summary for those items that are approved using the 510K process. If the product is exempt from FDA review and classification, please explain the basis for the exemption. Note: For drugs and biologicals only: FDA approval documentation may be submitted after the code application, but no later than March 31, 2009, provided all other application materials are complete and submitted by the deadline, and provided the application for marketing approval has been submitted to the FDA by March 31, 2008. Applicants awaiting FDA approval for drugs or biologicals at the January 5th submission deadline must submit with the application documentation evidencing submission for FDA approval, along with the date the application was submitted to the FDA. For all non-drug and biological items, the applicant must submit 3 months of marketing experience following the FDA approval date.

12. When was the item/product marketed in the United States? **Note** Marketing data is not required for drugs and biologicals, however; the date of first sale is required. Prior to submitting this coding recommendation, what is the total number of units sold in the U.S. and the total dollar amount in sales (Medicare, Medicaid and private insurance)? Do not estimate or provide projections - the information provided must represent actual volume of sales for the product for the period of time indicated.

13. Identify the percent of use of the item across the following settings for all non-drugs/biologicals.
   Physician's Office: _______
   Freestanding Ambulatory Care Clinics: _______
   Patient's Home by patient: _______
   Patient's Home by Health Care Provider: _______
   Nursing Home/Skilled Nursing Facility: _______
   Hospital Inpatient Facilities: _______
   Hospital Outpatient Facility: _______
   Other- (identify): _______
   **TOTAL VOLUME OF USE ACROSS ALL SETTINGS SHOULD EQUAL 100%**

14. What is the Manufacturer’s Suggested Retail Price (MSRP) or list price of the item? This question must be answered for all items, except drugs/biologicals.
HCPCS Coding Recommendation submitted by:
* Please provide a complete mailing address and direct dial phone number. We use this information to contact applicants regarding upcoming meetings, questions regarding applications, and to make notifications of the status of applications. Name: Name of Corporation/Organization: Mailing Address (street): City, State, Zip Telephone Number and extension: FAX Number: E-Mail Address: I attest that the information provided in this HCPCS coding recommendation is accurate and correct to the best of my knowledge. Date: _______________________________ _________________________
Signature of Applicant Is applicant the manufacturer? Y/N If not, the manufacturer must sign the following attestation: I attest that the information describing the product is accurate. ____________________________ ___________________________
Date: ________________________ Signature of Manufacturer

According to the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number. The valid OMB control number for this information collection is 0938-1042. The time required to complete this information collection is estimated to average 11 hours per response, including the time to review instructions, search existing data resources, gather the data needed, and complete and review the information collection. If you have comments concerning the accuracy of the time estimate(s) or suggestions for improving this form, please write to: CMS, 7500 Security Boulevard, Attn: PRA Reports Clearance Officer, Mail Stop C4-26-05, Baltimore, Maryland 21244-1850. Revised – 4/10/08
A company or individual has the option to submit a code request to the CMS by using a standard format which includes:

- Cover letter outlining the code request and briefly summarizing why the code is needed.
- Completely answer all questions located within Alpha-Numeric HCPCS Coding Recommendation Format Information Supporting Coding Modification Recommendation (see Appendix VIII.17).
- FDA approval letter.
- Supporting documentation and/or descriptive material to further understanding of the medical benefits of the item.
- No more than three samples of the product, video tapes or compact discs.
- Sign and date every recommendation.

The entirety of the packet must be 40 pages or less in length or they will not be considered for coverage. Each side of a piece of paper counts as one page so one must be very careful in being direct and to the point. Every question in the recommendation format must be completely answered; if there are any questions answered with N/A, then the application will automatically be discarded. The committee does not accept electronic copies; therefore the entire packet of information must be printed out and bundled securely. Binders and other bulky binding materials are not accepted. Besides conforming to these requirements, the requester must submit an additional 35 complete copies of the recommendation packet so that the entire committee may review the topic. These
recommendations have approximately an eleven-month turnaround period from the point when they are submitted to that when the requester receives an answer.
### Break-Even Analysis Chart with Preliminary Costs

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<th>Units of Sale</th>
<th>Fixed Cost</th>
<th>Total Cost</th>
<th>Total Revenue</th>
<th>Break-Even Point</th>
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</tbody>
</table>

**Break-Even Point**: The point at which Total Revenue equals Total Cost.
VIII.20 Break-Even Analysis Chart with Clinical Trials

The chart illustrates the break-even analysis with clinical trials. It shows the relationship between units of sale, dollars (fixed cost), total cost, and total revenue. The break-even point is indicated at the intersection of the fixed cost and total cost lines. The chart demonstrates how to determine the point at which the total revenue equals the total cost.