Evaluating the Cost Effectiveness of Using Lubricant Impregnated Surface Technology on Intravascular Catheters to Reduce Healthcare-Acquired Infections

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Abstract

This case study evaluates the cost effectiveness of developing lubricant impregnated surface technology (LIST)-coated intravascular catheters to decrease medical costs related to catheter-related blood stream infections (CRBSIs) and the associated patient morbidity and mortality in the two largest medical device markets, the United States (U.S.) and the European Union (E.U.). This analysis considers both the potential societal benefits (in terms of decreased morbidity and mortality and reduced healthcare costs) and the costs for an individual firm to secure regulatory approval. By using a cost effectiveness analysis (CEA) framework, this case study: identifies the possible outcomes of continuing to use standard catheters versus beginning to use LIS-coated catheters, estimates the probability and monetized cost of each possible outcome, and compares the expected value of each outcome.

In the societal-level analysis, the reduced probability of CRBSIs and associated cost savings are forecast by considering nine scenarios where efficacy of LIS-coated catheters ranges from 10 to 90 percent. In the 10 percent scenario, morbidity would be reduced by approximately 47,000 cases and mortality by approximately 8,000 cases, with total cost savings of approximately $1.6 billion in the U.S. and E.U. combined. In the 90 percent scenario, morbidity would be reduced by approximately 420,000 cases and mortality by approximately 72,000 cases, with total cost savings of approximately $14.0 billion in the U.S. and E.U. combined. This represents an average per-catheter savings ranging from $118 to $1,060.

The firm-level analysis forecasts that a catheter firm could realize additional annual revenues between $15.0 and $73.0 million for the combined U.S. and E.U. markets. The expected break-even period to recoup the initial costs of regulatory approval is two to six years in the E.U. and six to twelve years in the U.S.

Dedication

This effort is dedicated to my wife Carlie.

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Chapter I.

Introduction

This chapter introduces the thesis. Using a case study approach, this chapter uses a case study approach to describe the problem of interest, the hypothesis, and the objectives of the study.

Problem Statement

The use of intravascular catheters carries a sizable risk of infection leading to death and illness. The increasing need for intravascular catheters and the prolonged hospitalization and increased medical costs due to the resultant CRBSIs provide both a social and monetary incentive to develop catheters less prone to microbial infection. The aim of this case study is to quantify the costs associated with commercializing lubricant impregnated surface technology (LIST)-coated intravascular catheters, and to determine the potential market share and societal value that may be generated through their successful implementation. The results will help clarify if there is economic incentive for a firm or multiple firms to expend resources to market LIST-coated catheters. There are many factors to consider when trying to determine the feasibility of altering an existing medical device, including: development cost, clinical trial success and cost, reimbursement levels, and market uptake. This analysis will determine the cost effectiveness of seeking regulatory approval to commercialize LIST-coated catheters, which will be analyzed alongside potential economic and societal benefits of implementing LIST-coated catheters.

Central venous (intravascular) catheter (CVC) use, where catheters are used to deliver drugs and fluids near or directly into the heart, has become commonplace in inpatient and outpatient settings over the last several decades. Intravascular uses include "hemodynamic monitoring, renal replacement therapy, nutritional support, and medication administration" (Shah et al., 2013). Intravascular catheter use can be either short-term (less than thirty days) or long-term (30 or more days) (Food and Drug Administration, 1995). Unfortunately, the use of intravascular catheters carries a sizeable risk of infection. In the U.S., approximately 5.0 million patients require intravascular catheters each year, with an estimated 150,000 to 400,000 developing catheter-related blood stream infections (CRBSIs) (Frasca et al., 2010), which typically leads to an additional one to three-week stay in the hospital (Frasca et al., 2010) and between 500 and 4,000 deaths per year (Mermel, 2000).

There are several ways the use of CVCs can lead to infection. Insertion of the catheter can introduce microorganisms from the incision site, healthcare providers, or the hospital environment. In addition, the surface of the catheter can act as a site for bacterial colonization, leading to the development of antibiotic-resistant biofilms and the possibility of infection or clotting.

Three coating technologies have previously been suggested for implementation on intravascular catheters to try to reduce biofilm buildup and CRBSIs. The first is a hydrophilic coating that reduces adsorption of proteins and microorganisms. While there are many examples of proposed hydrophilic coatings, *in vitro* performance lacks efficacy and few survive clinical testing (Sousa et al., 2011). The second method coats the surface of the catheter with antimicrobials such as vanomycin or heparin. High dosages of the

antimicrobials are necessary to prevent bacterial colonization, leading to concerns of bacterial resistance (Sousa et al., 2011). In addition, it is difficult to regulate the antimicrobial dose, resulting in a large burst in the first few hours followed by a very low dose with low efficacy thereafter (Francolini et al., 2010). The third coating method consists of depositing silver nanoparticles on the surface of the intravascular catheter, with proponents of this method believing silver has antibiotic properties. The main drawback to this method is the lack of understanding on the antimicrobial mechanism of silver and the long-term consequences of using nanoparticles *in vivo* (Knetsch and Kool, 2011).

Preliminary research has shown that a new approach, LIST, offers the potential to reduce biofilm buildup and associated CRBSIs on intravascular catheters. A LIST coating is an extremely slippery surface that allows target liquids to slide freely on a solid surface by eliminating the no-slip boundary condition between the two. The coating introduces a mobile liquid lubricant that wicks through a textured solid and provides a liquid-liquid interface for the target liquid. Capillary forces generated from the engineered surface texture stabilize pockets of the mobile lubricating liquid. These liquid pockets move within the textured solid while providing a smooth liquid interface that greatly reduces the contact angle hysteresis of the target liquid on the surface. Additionally, LIST coatings can be made from a wide variety of chemistries which can enable the subsequent sliding of an extensive range of target liquids (including blood) (Quéré, 2005).

LIST coatings offer the potential for improving the efficacy and safety of intravascular catheters by preventing blood and its constituents from sticking to the

catheter. LIST has been shown to reduce biofilm accumulation by an order of magnitude on silicone tubing impregnated with silicone oil (MacCullum et al., 2014). In addition, LIST-coated shunts implanted in pigs have resulted in reduced biofilm formation and lowered incidence of thrombosis by lowering the adhesion of fibrin and platelets to the shunt (Leslie et al., 2014).

Coating performance is dependent on matching chemical properties of the lubricating liquid with the texture of the solid. When selecting a lubricating liquid, the liquid must (1) preferentially wet the textured surface, (2) remain immiscible with the target liquid, and (3) be slow to evaporate, to extend the life of the coating.

The physical properties of the textured solid surface play a crucial role in creating a slippery surface. Two primary parameters that influence the coating performance are roughness (r) and a solid fraction (ϕ). Roughness is calculated as the ratio between total surface area and projected surface area. The solid fraction is the proportion of solid that is exposed to the target liquid. Through these two purely physical parameters one can calculate the critical contact angle, θ_c, which will help inform whether or not a stable LIST will be created for the specific combination of surface, target liquid, and lubricating liquid. The critical angle θ_c can be calculated from the formula $\cos\ \theta_c\ = \frac{(1-\phi)}{(r-\phi)}$. (Quéré, 2008).

Functional LIST coatings require the lubricating liquid to preferentially wet the textured solid in the presence of the target liquid. When an interface exists between a liquid and a solid, the angle between the surface of the liquid and the outline of the solid surface is described as the contact angle. A contact angle of less than 90 degrees results in the liquid wetting out the solid, while contact angle greater than 90 degrees lead to the

liquid minimizing contact with the solid. The contact angle is dependent on the surface tensions of the solid, the liquid, and the surrounding phase (often, but not necessarily always, air). The surface tensions of interfaces solid/gas, solid/liquid and liquid/gas are γ_{SG}, γ_{SL} and γ_{LG} respectively. Young's equation describes the force equilibrium acting on a drop of the liquid: $\gamma_{SG}=\gamma_{SL}+\gamma_{LG}*\cos\theta$. If γ_{LG} is less than γ_{SG} the liquid will wet out the solid leading to a contact angle of 0 degrees through energy minimization.

The perceived advantages of coating intravascular catheters with LIS are threefold. First, while not yet tested clinically, LIST-coated surfaces should let the blood flow over the surface of the device unimpeded, reducing the risk of thrombosis, the need for anti-coagulants, and the associated health risks. LIST should reduce fibrin and platelets from the blood attaching to the indwelling catheter forming a blood clot. Blood clots can occlude healthy blood vessels, and may result in tissue death, heart attack, or stroke. Anticoagulants can be administered to reduce clotting, or the catheter can be coated with an anticoagulant (typically heparin), but the use of anticoagulants often results in increased morbidity and mortality from post-operative bleeding (Leslie et al., 2014). Therefore, LIST coatings can prevent occlusion because they can prevent the attachment of the fibrin and platelets from forming blood clots within the catheters.

A second advantage is that LIST coatings could prevent microbial contamination of the catheter that could lead to thrombosis. Intravascular catheters without LIST-coatings adsorb proteins on the surface. These proteins attract microorganisms that may be introduced from three locations: contamination from handling by healthcare providers, skin microorganisms migrating from the incision site, and blood-borne planktonic microorganisms (Howell et al., 2014). The adsorbed microorganisms will increase in

number through attracting additional blood-borne microorganisms and through reproduction leading to infection. These bacteria are easier to treat than biofilms because they are initially susceptible to antimicrobial medications and the hosts immune response, but can cause infections nonetheless. LIST coatings would prevent microbial contamination and therefore reduce infections. Additionally, researchers at the Wyss Institute showed the LIST coating helped reduce thrombosis by lowering the adhesion of fibrin and platelets to the device. (Leslie et al., 2014).

A third advantage of LIST coatings is that they could inhibit the buildup of biofilms and the accompanying risk of CRBSIs (MacCallum et al., 2014). Once a critical number of microorganisms colonize the catheter, the gene expression of the microorganisms changes and the colony begins to secrete an extracellular polymeric matrix called a biofilm, consisting primarily of polysaccharides, which helps protect the colony from shear stress, antibiotic substances, and host immune response. As the biofilm continues to develop, the microorganisms alter their gene expression to meet the requirement of nutrient and oxygen transport in the anaerobic environment created by the biofilm matrix (Knetsch and Kool, 2011). These morphological changes lead to a colony that is highly resistant to antibiotics and host immune response. LIST coatings would prevent a colony from forming within the catheter and thus reduce the build-up of biofilms.

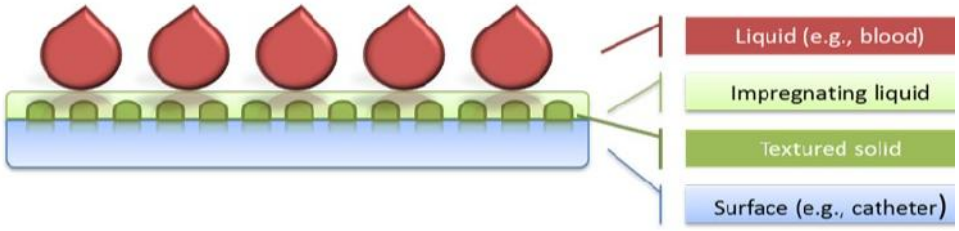

Figure 1. Lubricant Impregnated Surface Technology. This cartoon illustrates how a LIST coating allows blood to slide on a catheter surface without sticking.

Hypothesis

LIST-coated intravascular catheters should result in significantly lower patient morbidity and mortality and lower medical costs. The potential societal benefits (in terms of decreased morbidity and mortality) and cost savings (in terms of reduced hospital stays and need for medical care) will be considered alongside the costs associated for a firm to secure regulatory approval to sell the LIST-coated catheters. This case study will use a cost effectiveness analysis (CEA) framework to identify the possible outcomes of continuing to use standard catheters as compared to LIST-coated catheters, estimate the probability and monetized cost of each possible outcome, and compare the expected value of each outcome. The results should demonstrate that the LIST-coated catheters are worthwhile to pursue both on a societal level and individual firm level.

There are several factors that must be considered in estimating the cost-effectiveness of LIST-coated intravascular catheters:

1. **The total cost of CRBSIs caused by CVC use**, including the likely proportion of the total that can be reduced by LIST-coated catheters.

2. **The proportion of infections caused by biofilms as opposed to non-biofilm forming infections.** The initial microbial contamination is susceptible to antibiotic treatment or the host's immune response. If the initial microbial contamination is not controlled, the microorganism may create a biofilm in which the microorganisms' metabolism is altered and the colony is protected by an extracellular polymeric matrix. The biofilm is more resistant to antibiotics, especially those which target the microorganism's metabolic pathways.
3. **The probability and valuation of negative health outcomes associated with CRBSI**, such as extended hospital stays, increased morbidity, and mortality.
4. **The total volume of intravascular catheters and the market share that could be captured** by catheters coated with LIST.
5. **Other costs of market entry**, including obtaining regulatory approval and other factors that influence manufacturer and healthcare provider adoption.

By evaluating these factors using a CEA, the costs of implementing LIST-coated catheters can be weighed against the economic and health benefits to determine if the total cost savings and monetized benefits are enough to justify the costs of commercializing the application. The probability and cost parameters used in the analysis will be estimated using data gathered from peer-reviewed literature, United States government agency data, and information published by consulting firms.

If successfully commercialized, LIST-coated intravascular catheters that result in lower patient morbidity and mortality and lower medical costs may point the way to using LIST coatings to enhance other implantable medical devices and a virtually limitless number of applications.

Thesis Objectives and Organization

This case study will evaluate the business case of seeking regulatory approval to sell LIST-coated catheters. The first part of the analysis will consider costs at a societal level, comparing the expected value of the outcomes of health, excess morbidity and excess mortality between standard catheters and LIST-coated catheters. The second part of the analysis will consider costs from the perspective of a firm commercializing LIST-coated catheters, comparing the expected value of continuing to market standard catheters with the expected value of LIST-coated catheters. This firm-based analysis will consider the initial costs and payback period to recoup those costs. The expected values of both analyses will be considered to determine if there is incentive to seek regulatory approval to sell LIST-catheters. If the expected value of commercializing LIST-coated catheters is greater than the expected value of continuing to market existing catheters, then there may be a viable business case for a firm to undertake the project.

This case study will attempt to address the following items, focusing exclusively on the U.S. and E.U. catheter market:

1. Introduce materials and coatings used to manufacture catheters.
2. Describe incidence of CRBSIs.
3. Introduce Lubricant Impregnated Surfaces Technology.
4. Utilize a CEA to examine the feasibility of commercializing LIST-coated catheters.

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Chapter II.

Literature Review

The objective of this chapter is to provide an overview of catheters, their construction materials and coatings that have been used previously. It also provides an introduction to healthcare-acquired catheter infections, lubricant impregnated surface technology and an outline of the cost effectiveness analysis.

History of Catheters

An intravascular catheter is a small flexible tube inserted into a patient's vein to deliver medication, introduce fluids, or monitor vascular function. The use of catheters has improved patient care, which has stimulated the continuous development and improvement to catheter technology. The first modern catheter, called the "Rochester plastic needle," was developed in the Mayo Clinic in 1950 and consisted of polyvinyl chloride (PVC) tubing shrunk fit over a pair of steel needles. The "Angiocath" was later released by Deseret in 1964 as the first disposable catheter. Since 1969, catheters have been manufactured with non-toxic, slippery polytetrafluoroethylene (PTFE, commonly known as Teflon™) coatings which are easier to insert and safer for patients. Catheters with precision-milled tips that greatly improved patient comfort were introduced in 1974. The introduction of polyurethane catheters in 1983 helped reduce clotting and inflammation. (Rivera et al., 2005). Catheter technology continues to advance to this day

by incorporating newly developed polymers (Medical Device and Diagnostics Industry [MDDI], 2010).

Catheter Materials and Coatings

The most commonly used polymers for intravascular catheters are polyurethanes, fluoropolymers, polyolefins, polyimides, and polyether ether ketone (PEEK) (MDDI, 2010). The performance characteristics of an intravascular catheter depend on its constituent materials, which must meet a number of demands. Because the catheter is inserted into a slit in the skin and pushed into a vein with rotational force, a balance must be achieved between flexibility, pushability, rigidity, tensile strength, and compression resistance necessary to reach into distal areas of the body. The tip of the catheter must be soft enough to prevent damage to the blood vessels and surrounding tissue without collapsing (MDDI, 2013). The catheter must also have certain additional characteristics to aid the healthcare provider, as it must not be affected when sterilized prior to insertion and must be as radio-opaque as possible to assist in accurate implantation. Additionally, the catheter material must have certain chemical properties to ensure that it doesn't interfere with the body systems or medication. Specifically, catheter materials must be chemically stable, biocompatible, non-mutagenic, not alter any administered drugs, and not affect the blood vessels or blood. The choice of material can also affect the probability of infection. For instance, PTFE-coated and polyurethane catheters are associated with fewer infections than catheters made of PVC or polyethylene (Frasca et al., 2010; Sheth et al., 1983; Maki & Ringer, 1991).

Many catheters are coated, primarily as a means of combating infection. Three commercially available strategies exist for coating catheters to reduce protein and

microbial buildup, but none are without their drawbacks, and none have had a large impact on reducing infection. First, hydrophilic polymeric surface coatings are currently used to prevent the adsorption of proteins and subsequent microbial contamination on catheters. Hydrophilic surfaces attract water which sterically hinders the binding of proteins and makes it more difficult for bacteria to bind to the surfaces, which delays (but not entirely prevents) the onset of bacterial contamination (Knetsch and Kool, 2011). A second method is to coat the catheter with antimicrobial or antiseptic agents (e.g. gentamycin and minocycline). As with antibiotic use in other settings, there is a danger of creating antibiotic resistant "superbugs" with this application of antibacterial coatings. The third method is to coat the catheter with silver nanoparticles, which have been shown to have antimicrobial properties. The primary downside of this approach is that the safety of using nanoparticles in implanted devices is still unproven (Knetsch and Kool, 2011).

Healthcare-Acquired Catheter-Related Bloodstream Infections

Approximately 15.0 million intravascular catheters are used every year, as a routine part of medical care (Shah et al., 2013). Unfortunately, the use of these catheters can result in infections of the bloodstream as bacteria are introduced from outside the body and colonize along the catheter, sometimes leading to biofilms forming inside the catheter. The leading causes of CRBSIs are staphylococci (both *staphylococcus aureus* and the coagulase-negative staphylococci), enterococci, aerobic gram-negative bacilli and yeast (Shah et al., 2013).

There are four primary sources for bacteria being introduced from outside the body into the catheter. First and most common, the catheter tip can be contaminated with skin microorganisms at the incision site. The second most frequent source of

contamination is the healthcare workers handling the catheter. The third mode of contamination is uncommon, and results from bacteria spreading from another locus of infection within the patient's body. The fourth, and least common means of contamination is an infusate contamination from an improperly sterilized device (Treter and Macedo, 2011).

In some cases, especially when catheters are left in the body for several days, the bacteria populating the catheter form biofilms, which are communities of microorganisms that colonize a surface and develop an extracellular matrix that makes them resistant to antibiotics and phagocytosis. The irregular polymeric surfaces of intravascular catheters provide an ideal substrate for biofilms to grow. Once biofilms become established on a catheter, the usual solution is to remove the catheter and treat the infection, resulting in longer hospital stays and increased healthcare costs (Treter and Macedo, 2011).

CRBSIs have increased in number as the use of intravascular catheters has become commonplace. In the U.S., approximately 5 million patients require intravascular catheters each year with an estimated 3 to 8 percent of these patients (150,000 to 400,000) developing CRBSIs (Frasca et al., 2010). The Centers for Disease Control and Prevention (CDC) has provided a consistent estimate that lies in this range as well, at 250,000 patients developing CRBSIs each year (CDC, 2011). In intensive care units, intravascular catheters are the primary cause of healthcare-acquired blood infections, with between 40,000 (Zimlichman et al., 2013) and 80,000 (CDC, 2011) patients developing CRBSIs annually.

Patients with CRBSIs typically spend an additional one to three weeks in the hospital, and have increased mortality rates (Frasca et al., 2010), with between 500 and 4,000 patients dying each year as a result of CRBSIs (Mermel, 2000).

In addition to the human cost, CRBSIs result in higher treatment costs. The CDC (2011) estimates that the cost to treat an individual CRBSI ranges from $3,700 to $29,000, and Zimlichman (2013) estimates that the cost for cases in acute care units is even higher, at $45,000 per case. Estimates of the aggregate cost of treating CRBSIs in the U.S. each year range from $670.0 million to $2.7 billion (Scott, 2009), with Zimlichman (2013) putting the cost at $1.8 billion. In an effort to reduce costs and infections, the Centers for Medicare and Medicaid Services (CMS) is no longer providing reimbursement for the care of hospital-associated vascular catheter infections (Scott, 2009), so this burden falls on private insurers, hospitals, or the patients themselves.

The increasing need for intravascular catheters and the prolonged hospitalization and increased medical costs due to the resultant CRBSIs provide both an ethical and monetary incentive to develop catheters less prone to microbial infection.

Lubricant Impregnated Surface Technology

Lubricant impregnated surface technology (LIST) offers the potential for improving the efficacy and safety of intravascular catheters (Leslie et al, 2014). LIST have advantages over superhydrophobic surfaces because the air pockets in superhydrrohobic surfaces are subject to collapse under pressure, which results in a stickier surface. LIST addresses this concern by impregnating the rough surface with a lubricant. The lubricant is trapped on the textured surface, while remaining mobile within the surface through capillary forces. This reduces the no-slip boundary between a solid

and liquid and leads to greatly reduced contact angle hysteresis between the target liquid and the surface, which encourages sliding and increased mobility of the target liquid (Smith et al., 2013).

There is no universal LIST coating that repels all target liquids. Each coating is custom designed by calibrating the texture of the solid and the viscosity and chemistry of the lubricant to create a slippery surface that allows the target material to easily slide. Three critical properties of the lubricating liquid are that it wets the textured surface, doesn't evaporate under ambient conditions, and is immiscible with the target liquid. Two more characteristics must be considered to create an optimal LIST system. First, there is an inverse relationship between the viscosity of the lubricating liquid and the sliding speed of the viscous material. Second there may be shear forces acting on the liquid from fluid movement or mixing. If the lubricant is removed from the textured surface by shear, the surface is no longer slippery.

Experimental research has shown that medical tubing, catheters, and implantable devices have lower incidence of biofilm buildup with LIST. Researchers at the Wyss Institute have published data describing a ten-fold reduction in the incidence of biofilm formation on silicone tubing impregnated with silicone oil. The data was collected under flow conditions representative of the shear stress placed on inserted catheters (MacCullum et al., 2014). Another example of LIST technology is the coating of a perfluorocarbon on a medical shunt. When inserted in a pig the coating resulted in reduced biofilm formation.

Despite the potential of LIST demonstrated in these initial animal trials, no human trials have been conducted to date. The aim of this case study is to establish a business

case for commercializing LIST-coated catheters by quantifying the costs associated with commercializing LIS-coated catheters, in addition to determining the potential market share and societal value that may be generated with the successful implementation of LIST-coated catheters. The results will help clarify if there is economic incentive for a firm or firms to expend resources in the pursuit of developing and marketing LIST-coated catheters. With continued development, LIST could be implemented into intravascular catheters to reduce patient morbidity and mortality. There are many factors to consider when trying to determine the feasibility of altering an approved medical device, including manufacturing scale-up cost, clinical trial success and cost, reimbursement levels, and market uptake. This analysis will determine the cost effectiveness of the development project, which will be analyzed alongside potential economic and societal benefits of implementing LIST.

Cost Effectiveness Analysis Overview

Cost effectiveness analysis (CEA) is an economic evaluation used to compare the relative costs and outcomes associated with different courses of action. This type of analysis is frequently used to evaluate the costs and benefits of implementing novel medical technologies. Results from the CEA can inform policy and guidelines by providing a quantitative framework for deciding how to allocate resources to involved parties. CEA helps define the stakeholders involved in a decision and clarifies the costs, benefits, and risks associated with each stakeholder. There are three stakeholders considered in this study: catheter manufactures, patients, and society as a whole. First, the catheter manufacturer could profit by being able to sell their catheters at an increased price and/or capture additional market share by implementing LIST-coated catheters. The

catheter manufacturer assumes the upfront costs of trying to secure regulatory approval, which may or may not be successful. Second, the patient may benefit from lower incidence morbidity and mortality associated with CRBSIs. The patient may have higher out of pocket medical costs and carries the risk of being an early adopter of a new medical technology. Third, society can benefit from reduced CRBSI related healthcare cost and a healthier population. The societal cost could be unforeseen medical complications from adopting a novel technology.

There are potential drawbacks to using a CEA to make decisions. The primary drawback is that the output from the analysis is only as sound as the data entered into the model. The data used in this analysis is gathered from several hospitals and healthcare facilities throughout the E.U. and U.S. In addition to issues involved in aggregating and organizing large data sets, there are differences in definitions of terms and of data reporting requirements across these populations. The data used in this study is believed to be accurate at the time of source publication, but there is a lag time between when data is gathered and when it is published. Data used in this research has been collected from several peer reviewed journals, governmental and consulting sources. Every effort has been made to incorporate the best data available, but if there are errors present in the aggregated data sets than these errors will alter the results of this research.

Overview of Catheter Market

Intravascular catheters are used to treat medical conditions across the globe. There are four catheter manufacturing firms that account for approximately 88 percent of the market. The key manufacturers in this market are C.R. Bard, B. Braun Melsungen AG, Teleflex, Inc., and Vygon. Together these four companies control 88 percent of the

market. The global market for central venous catheters is estimated to be $649.0 million in 2015. There is a projected 5.1 percent compound annual growth rate (CAGR) over the next 10 years, which is expected to be driven by aging populations and advancements in antimicrobial coated catheters. (FMI, 2016b). The majority of novel medical devices are initially approved and adopted in the U.S. and E.U. before being adopted in other markets and this analysis will be limited to these two key markets.

There are approximately 4.0 million CVC units sold in the U.S. annually, generating approximately $238.0 million in revenue (ASD Reports, 2012; FMI, 2016a). There are two main types of CVC catheters: tunneled and implanted. Tunneled catheters have a portion left outside the skin whereas implanted ports are entirely subdermal and constituent the higher volume of catheters sold. These catheters vary in price, but the average retail catheter cost is $60 (ASD Reports, 2012; FMI, 2016a).

There are approximately 9.2 million CVC catheters sold in the E.U. annually generating $117.0 million in revenue. Growth in the European CVC market is driven primarily by the adoption of anti-microbial and anti-thrombogenic coatings on catheters. As in the U.S., there are implanted port and tunneled catheters with either single or multiple lumens that retail for an average price of $13 (FMI, 2016a; FMI, 2016b).

Regulatory Approval for Medical Devices

There are substantial differences in the requirements for acquiring regulatory approval for selling medical devices in the E.U. and U.S. The regulatory approval process in the E.U. attempts to integrate the individual regulatory systems of the member countries. The approval process in the U.S. is considerably longer and more expensive for all classes of medical devices compared to the E.U. In the U.S., on average, a Class III

device such as a catheter can take 54 months and costs $75.0 million in associated regulatory costs in the U.S. The same device averages an eleven-month approval time (Makower, 2010) and cost an average of $25.0 million (Harron, 2016) in the E.U.

In the U.S., in order to legally market a medical device it must be listed with the FDA to ensure the device is safe and effective. There are two possible paths to achieving FDA approval. The first is the 510(k) process which involves proving the device is substantially equivalent to a device that is already on the market. The second method is a premarket approval (PMA) which requires submitting clinical data supporting the safety and efficacy of the device. (Johnson, 2016) The premarket approval (PMA) is usually substantially more expensive and time consuming than the 510(k) application process.

There are three classes of medical devices Class I, Class II, and Class III. Class I devices are considered low risk and are subject to few regulatory requirements, such as dental floss. Class II devices carry a higher risk and are subject to more stringent regulatory control, condoms are an example. Both Class I and Class II devices can be submitted for FDA approval using the 510(k) processes. Class III devices carry the greatest risk and are subject to the strictest regulatory requirements. This process often requires clinical trials over one thousand participants at thirty to fifty sites. Almost all Class III devices must go through the PMA process. CVCs fall into this most stringent regulatory category, Class III.

Once a medical device is approved by FDA, the parent company is legally bound to maintain controls on manufacturing, labeling, adverse event reporting and device tracking. There are many different types of Class III medical devices, but on average, the

regulatory process for a new class III device can cost between $50.0 million and $100.0 million and take five years from prototype to PMA approval (Buntz, 2011).

In the E.U. medical devices must be granted a Conformité Européenne (CE mark) before they can legally be sold. Each individual member country has a Competent Authority, roughly analogous to the U.S. FDA, which oversees medical device approval. The composition, funding levels, and responsibilities of Competent Authorities varies widely between member countries. A medical device manufacturer can choose which country in the E.U. to seek regulatory approval and be granted a CE mark, and then gain access to the entire E.U. market.

Notified Bodies are third party organizations designated by an E.U. member country to evaluate products for conformity with E.U. regulations. They are designated by the Competent Authority to test for device performance and reliability. Complex medical devices, including Class III devices such as CVCs, are evaluated by Notified Bodies.

Unlike the U.S., the Notified Body system is for profit. The device manufacturer can choose which E.U. member country to seek approval in. This leads Notified Bodies to view manufacturers as customers and they compete with Notified Bodies in other countries for the manufacturers' business. For example, BSI, a Notified Body in the United Kingdom, writes in its advertising brochure "Our aim is to provide a high quality, fast, reliable, and stress-free service to meet your deadlines" (BSI Group, 2010).

The specific requirements for obtaining a CE mark is vague, not clearly defined and subject to interpretation. In general, the standard for receiving a CE mark is met if the medical device successfully performs as the manufacturer intends, and the proposed

benefits outweigh the potential risks (Kramer, 2012). Clinical trials are required for approval of high complexity medical devices such as CVC, but the results from these trials are not made public and are not binding once the device is approved. Based on data gathered in this study, the lower costs and clinical data requirements of regulatory approval in the European Union mean that approval should be sought there before the United States.

Chapter III.

Methods and Analysis

The purpose of this research is to determine the cost effectiveness of developing LIST-coated intravascular catheters to reduce medical costs related to CRBSIs and the associated patient morbidity and mortality. This case study contains two analyses: a societal-level analysis, and a firm-level analysis.

First, to evaluate societal benefits, this case study uses a CEA to identify the possible outcomes of continuing to use standard catheters, to estimate the probability and monetized value of each possible health outcome, and to compute the overall expected value of continuing to use standard catheters.

We then investigate the outcomes if LIST-coated catheters were to reduce the incidence of various negative health outcomes by 10 to 90 percent, estimating the range of reduced morbidity and mortality and resulting reduction in healthcare costs.

Second, to evaluate the incentives for a firm to adopt LIST, we compare the costs of seeking regulatory approval with the increased revenue stream captured with an increase in market share and/or increase in price. The results of these two analyses are used to determine if LIST-coated catheters are worthwhile to pursue both on a societal level and individual firm level.

Societal-Level CEA

For the societal-level analysis, a CEA will be used to evaluate clinical outcomes and healthcare costs associated with standard catheters, and estimate how these would change with LIST-coated catheters. The cost for a healthcare system to buy traditional catheters is relatively low, but traditional catheters are associated with healthcare-acquired infections, which have a high societal and monetary cost. The cost for LIST-coated catheters would be higher, but should be associated with less infection and a resulting reduction in negative health outcomes and costs. This analysis tests the proposition that LIST-coated catheters would result in better outcomes both societally (in terms of reduced morbidity and mortality) and financially (in terms of the costs to society as a whole for treating any resulting infections).

This case study used a literature review to gather data on the key inputs, such as market size, costs, and the probability of various health outcomes. The data gathered from the literature review is recorded and the calculations performed in an Excel spreadsheet.

The analysis begins with basic market information, summarized in Table 1, to estimate the number of CVCs used each year in the U.S. and E.U. The average price per standard catheter is determined by dividing the total CVC market revenue by the number of catheters sold. The three estimates presented from the literature represent high, medium and low values.

Next, the probability of developing a CRBSI is estimated using data from three types of sources:

1. Databases of peer-reviewed literature such as Pubmed, National Libraries of Medicine (NLM) and the National Institute of Health (NIH).
2. Data from hospitals participating in the National Healthcare Safety Network (NHSN) reported by the Centers for Disease Control and Prevention (CDC) and The European Centre for Disease Prevention and Control (ECDC).
3. Data on medical care costs reported by CMS.

The probabilities of health outcomes associated with the use of CVCs are summarized in Table 7. The possible outcomes evaluated include the following:

- Health (no excess morbidity or mortality associated with catheter use).
- Non-biofilm-associated CRBSI.
- CRBSI-associated morbidity.
- CRBSI-associated mortality.
- Biofilm.
- Biofilm-associated morbidity.
- Biofilm-associated mortality.
- Biofilm formation, but no adverse impacts (health).

The incidence of developing a CRBSI in the U.S. or E.U. is calculated using the data in Table 6 and Table 7. The number of cases of each health outcome are calculated by multiplying the number of catheters used by the probability of each health outcome, summarized in Table 8. As a simplifying assumption, the calculations assume that each patient uses only one catheter, not multiple catheters during their treatment.

The CVC procedure cost is a baseline charge incurred regardless of the health outcome. If the patient develops an infection, there are additional expenses incurred to

treat the infection. The amount of additional expense is dependent on several factors including the type and severity of the infection, length of hospital stays required, and geographical healthcare costs.

The costs associated with the basic CVC procedure and treating catheter related morbidity and mortality are estimated from the following type of sources:

1. Data on medical care costs reported by CMS.
2. Reports from the Joint Commission (JC) and Healthcare Infection Control Practices Advisory Committee (HICPAC).
3. Data published by patient safety groups including the Pennsylvania Patient Safety Authority (PPSA) and the Association for Professionals in Infection Control and Epidemiology (APIC).
4. Peer-reviewed literature from medical and scientific journals including Clinical Infectious Diseases and Infection Control Today.

The data listed in Table 9 show national averages for the U.S. or E.U. derived from these data sources. The CVC insertion and monitoring procedure averages $1,317 in the U.S. (Bard, 2010) and $1,436 in the E.U. (Biffi, 2014). If an infection occurs, the supplemental costs to treat the infection averages $47,333 in the U.S. (Zimlichman, 2013) and $17,333 in the E.U. (Gahlot, 2014; Tacconelli, 2009; ECDC, 2013; Hu, 2004).

There are also additional costs if the patient dies from complications related to the infections. The costs associated with mortality are calculated by multiplying the statistical value of human life with the percentage of mortality directly related to CRBSI, and average $8.0 million in the U.S. (Doucouliagos, 2014) and $2.8 million in the E.U. (WHO, 2014).

The cost per patient in each of these scenarios is then calculated by summing the relevant costs, e.g., summing the insertion and morbidity costs for patients where infection occurs, and summing the insertion and mortality costs for patients where mortality occurs.

The expected monetary value for each health outcome is determined by multiplying the cost of each outcome by the probability of it occurring, and then the overall expected value is calculated by summing over these outcomes. Finally, the aggregate costs for the CVC procedure and associated health outcomes in the U.S. and E.U. are calculated by multiplying the number of patients with each health outcomes (from Table 8) by the average cost per patient (from Table 9). The resulting aggregate societal cost of using traditional CVCs is summarized in Table 10.

Firm-Level Analysis

To analyze the incentives and disincentives for an individual catheter firm to adopt LIST-coated catheters, this case study analyzes and compares the up-front costs and future income flows associated with standard catheters and LIST-coated catheters, which will be used to calculate the payback period for the firm to recoup their initial investment. There are several steps to commercializing LIST-coated catheters, including scaling the LIST application, obtaining regulatory approval, and successfully marketing the LIST-coated catheter to healthcare providers. This study evaluates the regulatory costs associated with commercializing LIST-coated catheters. The scaling and marketing costs are assumed to be rolled into the catheter firm's existing cost structure.

Three types of sources are used to consider the costs of achieving regulatory approval to sell LIST-coated catheters:

1. Consulting firm and market reports, such as those published by Boston MedTech Investors and Boston Consulting Group.
2. FDA's Premarket Approval guidance for medical devices.
3. Reports from the Congressional Research Service (CRS).

Three types of sources are used to help determine how regulatory approval costs factor into LIST-coated catheter uptake:

1. A survey of 200 medical device manufacturers on the costs of bringing a device to market.
2. U.S. Food and Drug Administration Publication Overview of Device Regulation.
3. Peer-reviewed literature on the cost of obtaining medical device approval in the U.S., including Makower, et al.'s (2010) estimate of device development costs.

The regulatory approval costs for the LIST-coated catheter are directly related to the cost the manufacturer must charge for the catheter firm to recoup their costs. Table 1 shows the average approval time for medical devices in the U.S. and E.U. and average cost of seeking approval in each market.

Table 1. Average Time and Costs to Achieve Regulatory Approval.

	Values	Sources
U.S.		
FDA Approval Time PMA (months)	54	Makower, 2010
FDA Approval Cost	$75,000,000	Makower, 2010
E.U.		
EU Approval Time (months)	11	Makower, 2010
EU Approval Cost	$25,000,000	Harron, 2016

While the maximum unit price a firm could charge for LIST-coated catheters cannot be predicted with accuracy at this stage, the costs associated with CRBSIs are used to forecast the *potential* revenue that could be generated by the catheter firm by adopting LIST-coated catheters. This implicitly assumes that healthcare systems will be willing to spend at least some portion of the money they would have spent treating catheter-related infections on LIST-catheters that prevent those infections from occurring in the first place.

The analysis is based on the following assumptions surrounding the catheter company, regulatory approval time and costs:

1. A major catheter manufacturing firm licenses existing LIST technology from a coatings company.
2. The catheter manufacturer is assumed to control 22 percent of the E.U. and U.S. catheter markets. This is based on market reports which indicate the top four catheter manufacturers control eighty-eight percent of the market (FMI, 2016a), and an assumption that they compare equal shares (88 percent divided by four companies equals 22 percent each).
3. The regulatory approval process in the U.S. for a Class III medical device averages 54 months and costs $75.0 Million (Makower, 2010).
4. The regulatory approval process in the E.U. for a Class III device averages 11 months, with an average cost of $25.0 Million (Boston Consulting Group, 2012; Makower, 2010).
5. LIST-coated catheter will increase the cost of the catheter itself, but not the labor costs associated with the insertion procedure.

The analysis then models a conservative, moderate and aggressive scenario to examine the risks and benefits of licensing LIST technology. These vary the amount a firm can increase the catheter price and/or the amount of market share they are able to capture with LIST-coated catheters.

1. The **conservative** scenario is based on the catheter manufacturing firm capturing and additional 20 percent market share by implementing LIST-coated catheters (Snowbeck, 2008).
2. The **moderate** scenario is based on the catheter manufacturing firm increasing the price of the LIST-coated catheter by 74 percent over the standard catheter pricing. (Harron, 2016).
3. The **aggressive** scenario assumes the catheter firm realizes both a market share increase of 20 percentage points and a price increase of 74 percent by implementing LIST-coated catheters.

For each of these three scenarios, we calculate the payback period, i.e., how long it would take for a firm licensing the LIST-coated catheter technology to recoup their initial investment. The initial phase includes cost outlays for obtaining regulatory approval. Once approval is obtained, the company begins earning increased revenue and/or capturing increased revenue as they market the LIST-coated catheter.

Chapter IV.

Results

LIST-coated intravascular catheters should result in significantly lower patient morbidity and mortality and lower medical costs. To test the hypothesis, this case study evaluates the data gathered during the literature review using two analyses: a societal-level analysis, and a firm-level analysis. The societal-level analysis uses a CEA to evaluate clinical outcomes and healthcare costs associated with standard catheters and estimate how these would change with LIST-coated catheters. The firm level analysis evaluates the business case for a firm to bring LIST-coated catheters to market, weighing the up-front costs of obtaining regulatory approval against the future revenues that could be generated by the catheter firm from capturing additional market share and/or an increase in sale price.

Societal-Level Analysis

For the societal-level analysis, clinical outcomes and healthcare costs associated with standard catheters are estimated and then compared to potential clinical outcomes and healthcare costs with LIST-coated catheters. The analysis begins by determining the value of the central venous catheter market, which is $238.0 million in the U.S. and $117.0 million in the E.U. Next, the probability for each health outcome is estimated using a literature review (see Table 7). The probability of each health outcome (from

Table 7) is then multiplied by the associated unit cost of each outcome (summarized in Table 8), to give the aggregate societal cost for each outcome (as shown in Table 10).

There are no commercially available LIST-coated catheters to date, but LIST-coated catheters are expected to lower the incidence of CRBSIs, biofilm development and the associated medical costs. The reduced probability of CRBSIs and associated cost savings are forecast by considering nine scenarios where LIST-coated catheters have varying degrees of efficacy, ranging from 10 percent to 90 percent in 10 percentage point increments. Table 11 details the reduction in morbidity and mortality and the associated cost savings from adopting LIST-coated catheters for the 10 percent and 90 percent scenarios.

In the most conservative scenario, where LIST-coated catheters reduce CRBSIs by 10 percent, morbidity is reduced by approximately 15,106 cases in the U.S. and 31,571 cases in the E.U., for a combined total of 46,676 cases. The reduced healthcare costs associated with this reduction in morbidity are $735.0 million in the U.S. and $593.0 million in the E.U. for a combined total of $1.3 billion. Mortality is reduced by approximately 2,827 in the U.S. and 5,139 in the E.U., for a combined total of 7,967 cases. The monetized value of this reduction in mortality is $139.0 million in the U.S. and $93.0 million in the E.U. for a combined total of approximately $233.0 million.

In the most aggressive scenario, where LIST-coated catheters reduce CRBIs by 90 percent, morbidity is reduced by approximately 136,000 cases in the U.S. and 284,000 cases in the E.U., for a combined total of 420,000 cases. The reduced healthcare costs associated with this reduction in morbidity are $6.6 billion in the U.S. and $5.3 billion in the E.U. for a combined total of $11.9 billion. Mortality is reduced by approximately

25,000 in the U.S and 46,000 in the E.U., for a combined total of 72,000 cases. The monetized value of this reduction in mortality is $1.3 billion in the U.S. and $838.0 million in the E.U., for a combined total of approximately $2.1 billion.

Summing the cost savings associated with morbidity and mortality for the 10 and 90 percent scenarios, respectively, the use of LIST-coated catheters could save between $874.0 million and $7.9 billion in the U.S., and $686.0 million and $6.2 billion in the E.U., and between $1.6 billion and $14.1 billion in both markets combined.

In addition to considering the extreme cases, where LIST-coated catheters reduce CRBSIs by 10 and 90 percent, we also consider several intermediate cases, where CRBSIs are reduced in additional 10 percentage point increments (20 percent, 30 percent, etc.). Figure 2 shows the range of potential reductions in the annual incidence of morbidity in the U.S. and E.U. for both biofilm-associated and non-biofilm-associated CRBSIs, and Figure 3 shows the associated reduction in healthcare costs. Figure 4 shows the range of potential reductions in the annual incidence of mortality in the U.S. and E.U. for both biofilm-associated and non-biofilm-associated CRBSIs and Figure 5 shows the monetized value of this reduction in mortality.

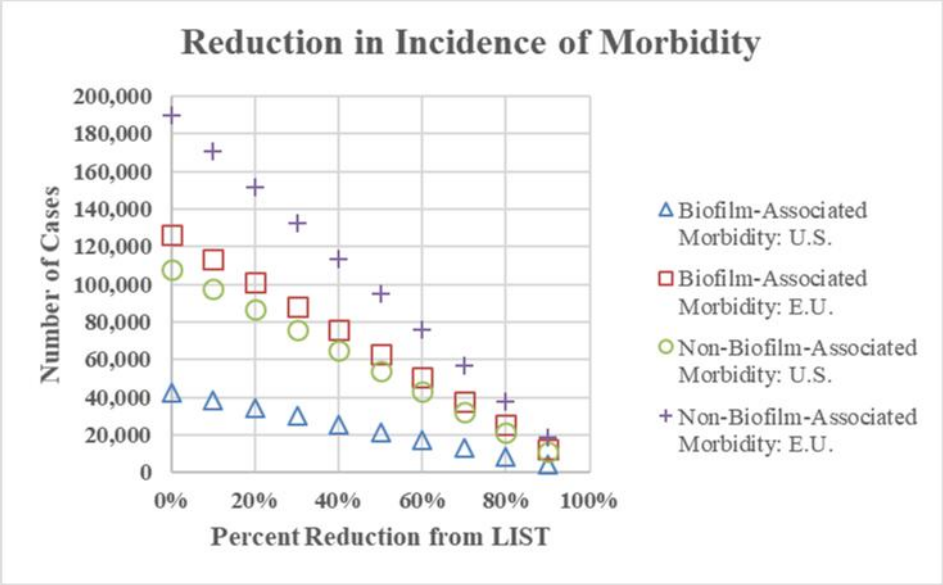

Figure 2: Reduction in Incidence of Morbidity. This figure shows the range of potential reductions in the annual incidence of morbidity in the U.S. and E.U. for both biofilm-associated and non-biofilm-associated CRBSIs.

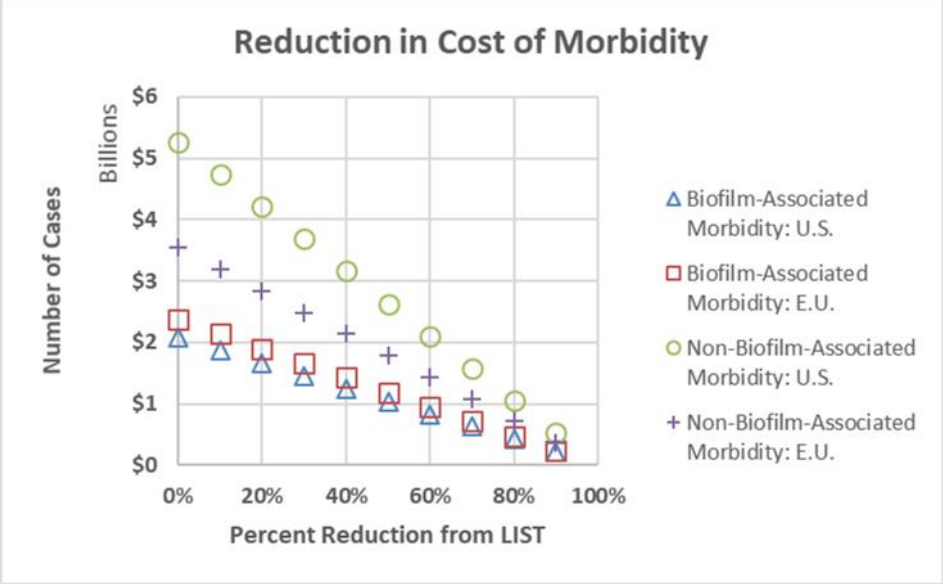

Figure 3: Reduction in Cost of Morbidity. This figure depicts the range of potential reductions in healthcare costs in the U.S. and E.U. for both biofilm and non-biofilm-associated CRBSI morbidity.

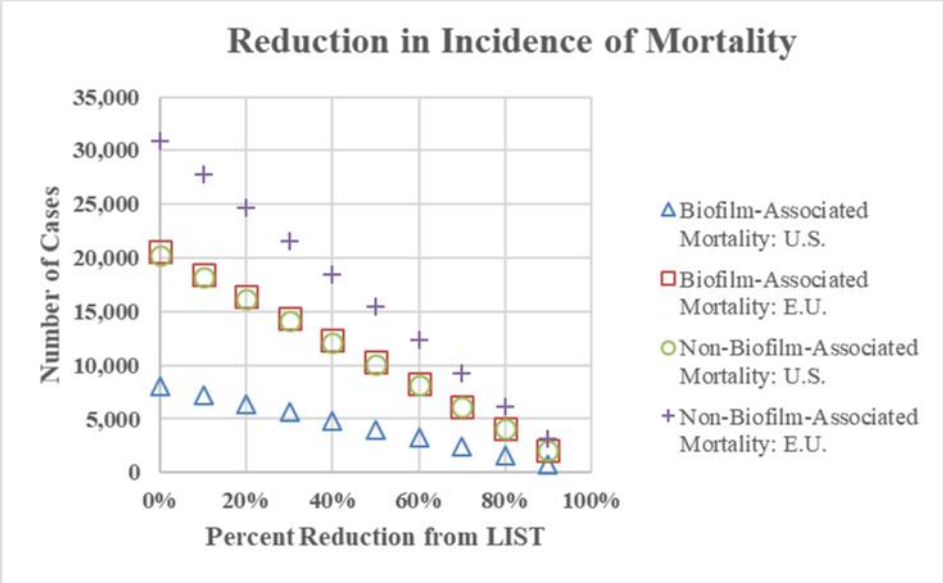

Figure 4: Reduction in Incidence of Mortality. This figure illustrates the range of potential reductions in the annual incidence of mortality in the U.S. and E.U. for both biofilm-associated and non-biofilm-associated CRBSIs.

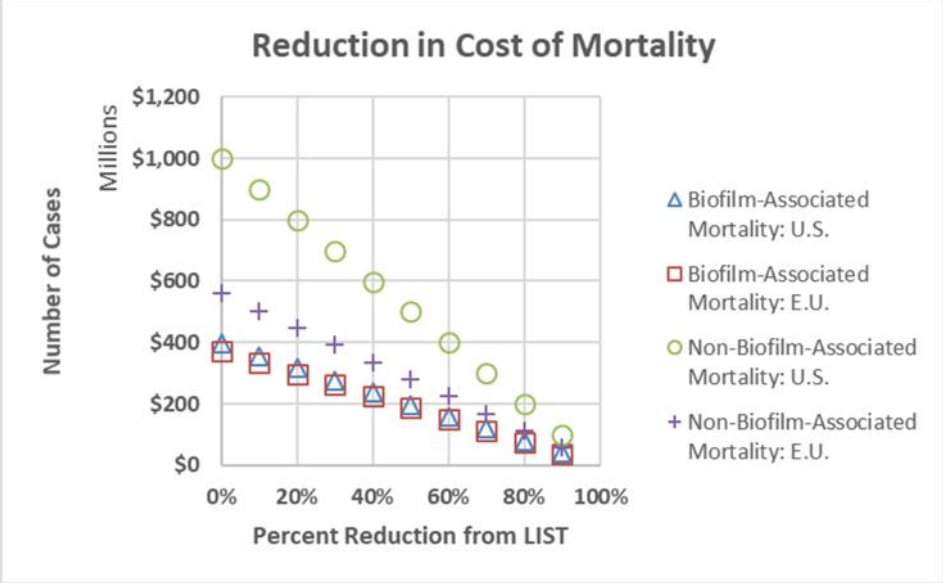

Figure 5: Reduction in Cost of Mortality. This figure shows the range of potential reductions in healthcare costs in the U.S. and E.U. for both biofilm and non-biofilm-associated CRBSI mortality.

In sum, this analysis finds that LIST-coated catheters have the potential to reduce CRBSI-associated morbidity by 47,000 to 420,000 cases per year and mortality by 8,000 to 71,000 cases per year, with an associated cost savings of $1.6 billion to $14.1 billion per year, or $118 to $1,060 per catheter. This is higher than other studies have found for catheters coated with a combination of the antimicrobials chlorhexidine and silver sulfadiazine, which are designed to inhibit the colonization of bacteria on the catheter surface. The antimicrobial coated catheters resulted in savings $68 to $391 per catheter, or approximately $98 to $562 in 2017 dollars (Veenstra, 1999; BEA, 2017).

We next perform a cost effectiveness analysis which compares the relative costs and outcomes of different courses of action. The costs for using a CVC consist of the catheter cost, procedure cost, and the additional healthcare cost if a CRBSI develops. The catheter cost whether of standard or LIST-coated and procedure cost will be incurred no matter what, but CRBSI-related healthcare costs can be avoided. The baseline costs for using traditional CVCs are summarized in Table 12. The infection-related cost per patient is determined by dividing the treatment cost by the number of catheters used. Using traditional catheters, the average infection-related cost per catheter is $2,127 in the U.S., $685 in the E.U., and $1,120 in the U.S. and E.U. combined.

LIST-coated catheters would be more expensive than traditional catheters. This analysis assumes a 74 percent increase in the retail price of the catheters (which would cover the cost of development, obtaining regulatory approval, and profit for the firm). With this price increase, the incremental cost for each LIST-coated catheter would be $44 in the U.S. and $10 in the E.U. This increased catheter price is weighed against LIST-

coated catheters' ability to reduce CRBIs and the associated healthcare costs to determine if LIST is a viable business opportunity.

This cost-effectiveness analysis considers two scenarios, where LIST-coated catheters reduce CRBIs and treatment costs by 10 and 90 percent compared to traditional catheters. The 10 percent reduction scenario results in per-catheter infection-related costs of $1,914 in the U.S., $616 in the E.U., and $1,008 in the U.S. and E.U. combined, summarized in Table 13. The 90 percent scenario reduction scenario results in per catheter infection costs $213 in the U.S., $153 in the E.U., and $171 in the U.S. and E.U. combined, summarized in Table 14.

Comparing the costs in the 10 and 90 percent reduction scenarios to the baseline, in the U.S. costs are reduced by $213 to $914 per catheter, and in the E.U. costs are reduced by $68 to $514 per catheter. (U.S. and E.U. per catheter infection related savings are summarized in Table 2.) These reductions in the average cost of treating CRBSIs per catheter far outweigh the increased unit cost of an LIST-coated catheter, $44 in the U.S. and $10 in the E.U. These results suggest that LIST-coated catheters would result in net savings for purchasers (such as hospitals), payers (who provide reimbursement), and to society as a whole (which would see reduced morbidity and mortality), supporting the hypothesis of this study.

Table 2: Infection Related Costs Savings from LIST-coated Catheters

	Traditional	**10% Reduction LIST**	**Treatment Savings**	**90% Reduction LIST**	**Treatment Savings**
U.S.	$2,127	$1,914	$213	$213	$1,914
E.U.	$685	$616	$68	$153	$532
U.S. and E.U.	$1,120	$1,008	$112	$171	$949

Firm-Level Analysis

The purpose of the firm-level analysis is to evaluate the business case for a catheter firm to bring LIST-coated catheters to market. Marketing a new medical device would require large initial costs to obtain regulatory approval, but should result in increased revenue in subsequent years. The analysis models a conservative, moderate, and aggressive scenario to compare the regulatory costs to anticipated future payments to calculate the break-even period to recoup the initial investment.

The **conservative** scenario is based on the catheter manufacturing firm capturing an additional 20 percent of market share by bringing LIST-coated catheters to market (Snowbeck, 2008). In the U.S., the market for central venous catheters is valued at $238.0 million (FMI, 2016b; ASDS Reports, 2012), and each of the four large catheter companies is estimated to have a 22 percent market share (FMI, 2016b), for current revenues of $52.4 million each (22 percent of $238.0 million). A 20 percent increase in market share would translate into an additional $10.5 million in revenue (20 percent of $52.4 million).

In the E.U., the market for central venous catheters is valued at $117.0 million (FMI, 2016a; FMI, 2016b), and each of the four large catheter companies is estimated to have a 22 percent market share (FMI, 2016b), for current revenues of $25.7 million each (22 percent of $117.0 million). A 20 percent increase in market share would translate into an additional $5.2 million in revenue (20 percent of $25.8 million).

For the U.S. and E.U. combined, a firm gaining a 20 percent increase in market share would see increased revenues of $15.6 million per year, detailed in Table 3.

Table 3: Conservative Scenario: Market Share Capture

	Values	Sources
U.S.		
Catheter Market Size	$238,000,000	FMI, 2016b; ASDS Reports, 2012
Current Market Share Percent	22%	FMI, 2016b
Current Revenue	$52,360,000	FMI, 2016b; ASDS Reports, 2012
Market Share Captured with LIS Catheter	20%	Harron, 2016
Additional Revenue from LIST Catheter	$10,472,000	FMI, 2016b; ASDS Reports, 2012; Harron, 2016
E.U.		
Catheter Market Size	$117,000,000	FMI, 2016a; FMI, 2016b
Current Market Share Percent	22%	FMI, 2016b
Current Revenue	$25,740,000	FMI, 2016a; FMI, 2016b; Harron, 2016
Price Increase Captured from LIST Catheter	20%	Harron, 2016
Additional Revenue from LIST Catheter	$5,148,000	FMI, 2016a; FMI, 2016b; Harron, 2016
U.S. and E.U.		
Additional Revenue from LIST Catheter	$15,620,000	FMI, 2016a; FMI, 2016b; ASDS Reports, 2012; Harron, 2016

The **moderate** scenario is based on the catheter manufacturing firm increasing the price of the LIST-coated catheter by 74 percent over the standard catheter price (Harron, 2016). In the U.S., the market for central venous catheters is valued at $238.0 million (FMI, 2016b; ASDS Reports, 2012), and each of the four large catheter companies is estimated to have a 22 percent market share (FMI, 2016b), for current revenues of $52.4 million each (22 percent of $238.0 million). A 74-percentage point increase in catheter price would translate into an additional $38.7 million in revenue (74 percent of $52.4 million).

In the E.U., the market for central venous catheters is valued at $117.0 million (FMI, 2016a; FMI 2016b), and each of the four large catheter companies is estimated to have a 22 percent market share (FMI, 2016b), for current revenues of $25.7 million each

(22 percent of $117.0 million). A 74 percent increase in the price per catheter would translate into an additional $19.0 million in revenue (74 percent of $25.7 million).

For the U.S. and E.U. combined, a firm gaining a 74 percent increase in catheter sales would see increased revenues of $57.8 million per year, detailed in Table 4.

Table 4: Moderate Scenario: Price Increase

	Values	Sources
U.S.		
Catheter Market Size	$238,000,000	FMI, 2016b; ASDS Reports, 2012
Market Share of Catheter Firm	22%	FMI, 2016b
Current Revenue	$52,360,000	FMI, 2016b; ASDS Reports, 2012
Price Increase Capture from LIST Catheter	74%	Snowbeck, 2008
Additional Revenue from LIST Catheter	$38,746,400	FMI, 2016b; ASDS Reports, 2012; Snowbeck, 2008
E.U.		
Catheter Market Size	$117,000,000	FMI, 2016b; FMI, 2016a
Market Share of Catheter Firm	22%	FMI, 2016b
Current Revenue	$25,740,000	FMI, 2016b; FMI, 2016a
Price Increase Capture from LIST Catheter	74%	Snowbeck, 2008
Additional Revenue from LIST Catheter	$19,047,600	FMI, 2016a; FMI, 2016b; Snowbeck, 2008
U.S. and E.U.		
Additional Revenue from LIST Catheter	$57,794,000	FMI, 2016a; FMI, 2016b; ASDS Reports, 2012; Harron, 2016

The **aggressive** scenario assumes the catheter firm realizes both a market share increase of 20 percent and a price increase of 74 percent by implementing LIS-coated catheters (i.e., the conservative and moderate scenarios are combined. In the U.S., $10.5 million of additional revenues are generated from the increased market share capture and $38.7 million incremental revenues are generated from sales price increase for a total of $49.2 million of increased revenues.

In the E.U., market share capture results in $5.2 million of additional revenues and $19.1 million of additional revenues are generated from sales price increase, for a total of $24.2 million of increased revenues.

For the U.S. and E.U. combined, a firm gaining a 20 percent increase in market share and 74 percent increase in catheter prices would result in increased revenues of $73.4 million per year, as summarized in Table 5. Based on this analysis, a catheter manufacturing firm should attempt to achieve regulatory approval LIST-coated catheters in the E.U. before the U.S. It is most profitable for the catheter firm to both seek increases in market share and price, but if both strategies can't be pursued, then a price increase will result in greater revenues than a market share increase.

Table 5: Aggressive Scenario: Market Share Capture and Price Increase

	Additional Annual Revenue	Sources
U.S.		
Conservative Scenario	$10,472,000	FMI, 2016b; ASDS Reports, 2012; Harron, 2016
Moderate Scenario	$38,746,400	FMI, 2016b; ASDS Reports, 2012; Snowbeck, 2008
Aggressive Scenario	$49,218,400	FMI, 2016b; ASDS Reports, 2012; Snowbeck, 2008; Harron, 2016
E.U.		
Conservative Scenario	$5,148,000	FMI, 2016a; FMI, 2016b; Harron, 2016
Moderate Scenario	$19,047,600	FMI, 2016a; FMI, 2016b; Snowbeck, 2008
Aggressive Scenario	$24,195,600	FMI, 2016a; FMI, 2016b; Snowbeck, 2008; Harron, 2016
U.S. and E.U.		
Aggressive Scenario	$73,414,000	FMI, 2016a; FMI, 2016b; ASDS Reports, 2012; Harron, 2016

For each of these three scenarios, we calculate the payback period, i.e., how long it would take for a firm licensing the LIST-coated catheter technology to recoup their initial investment. The initial investment is the time and costs associated with achieving regulatory approval before the LIST-coated catheter can be sold for additional revenues. The average time and costs to secure regulatory approval for a Class III device is $25.0 million over 11 months in the E.U. and $75.0 million over 54 months in the U.S. Many device manufacturers initially seek regulatory approval in the E.U. before the U.S. due to the lower costs and shorter approval times.

The break-even time is determined by how long it takes for the incremental revenues from adopting LIST-coated catheters to equal the initial investment of seeking regulatory approval. There are no additional revenues for 54 months in the U.S. and 11 months in the E.U. during the regulatory approval process. The average increased monthly revenues from LIST-coated catheters in the U.S. are $873,000 in the conservative scenario, $3.2 million in the moderate scenario, and $4.1 million in the aggressive scenario. The break-even period for the conservative scenario in the U.S is 140 months ($75.0 million, the cost of seeking regulatory approval, divided by $873,000, the increased monthly revenues, plus the 54 months it takes to achieve regulatory approval). Following the same analysis, the break-even periods for the moderate and aggressive scenarios are 78 months and 73 months, respectively. These streams of revenue over time is illustrated in Figure 6.

In the E.U., the average monthly increased revenues from LIST-coated catheters are $429,000 in the conservative scenario, $1.6 million in the moderate scenario, and $2.0

million in the aggressive scenario. In the conservative scenario, the break-even period is 70 months ($25.0 million for regulatory approval divided by $429,000.0 in increased monthly revenue plus 11 months for regulatory approval). Likewise, a catheter company in the E.U. could expect to break-even in 27 and 24 months in the moderate and aggressive scenarios, respectively. These streams of revenues are summarized in Figure 7.

Summarizing the calculations above, the expected break-even period to recoup the initial costs of regulatory approval ranges from two to six years in the E.U. and six to 12 years in the U.S. These results suggest that there is economic benefit for a catheter firm to seek regulatory approval for LIST-coated catheters in the E.U. before the U.S. The firm could use the revenues generated and the clinical data gathered in the E.U. to support product launch in the U.S.

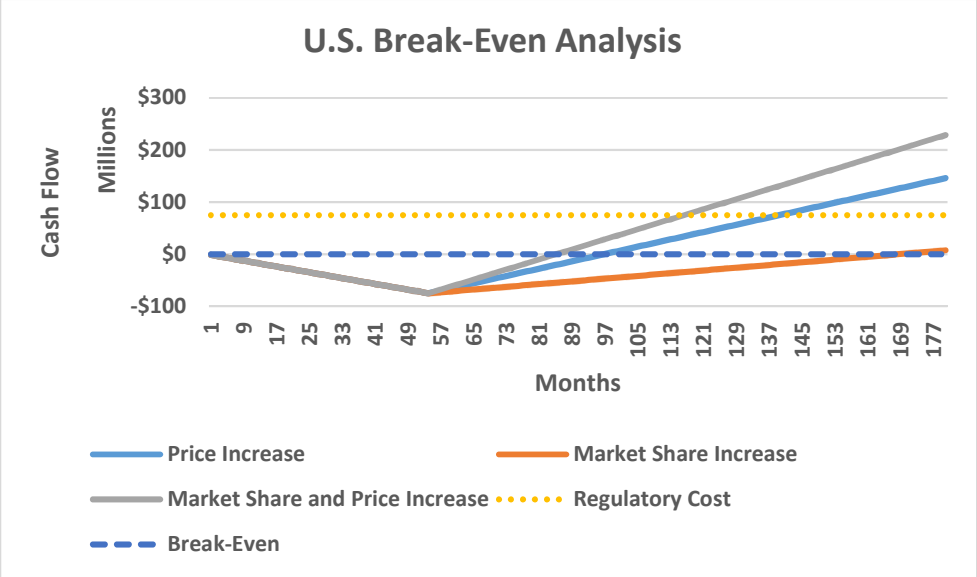

Figure 6: U.S. Break-Even Analysis. This figure depicts the break-even period in the U.S. for the conservative, moderate and aggressive scenarios, i.e. the point at which the cost savings equals the initial investment in LIST technology.

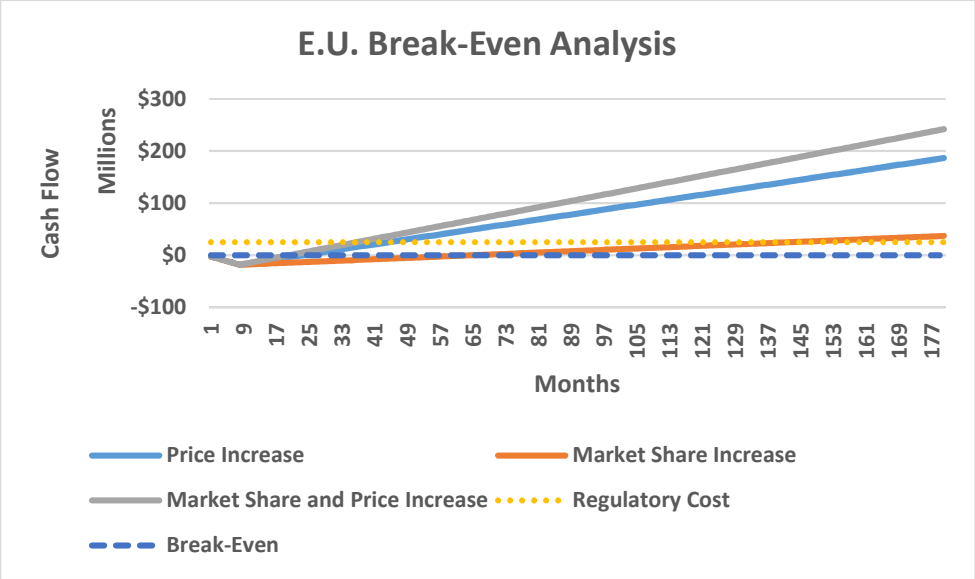

Figure 7: E.U. Break-Even Analysis. This figure depicts the break-even period in the E.U. for the conservative, moderate and aggressive scenarios, i.e. the point at which the cost savings equals the initial investment in LIST technology.

Chapter V.

Discussion

This chapter provides a summary of the case study findings including the societal and firm level analyses for adopting LIST-coated catheters. In addition, challenges and limitations of this study will described as well as the further implications of the conclusions generated in this research.

Summary of Case Study Findings

This case study evaluates the economics of developing LIS-coated catheters. The first of two analyses focuses on the societal benefits of using LIST-coated catheters (in terms of decreased morbidity and mortality) and cost savings (in terms of reduced hospital stays and need for medical care). This analysis uses a CEA framework to identify the possible outcomes of continuing to use standard catheters as compared to LIST-coated catheters, estimates the probability and monetized cost of each possible outcome, and compares the expected value of each outcome. The second analysis examines the business case and considers the costs associated for an individual firm to secure regulatory approval to sell the LIST-coated catheters, and compares this to the increased future revenues from selling LIST-coated catheters.

The societal analysis assumes that using LIST-coated catheters would reduce CRBSIs by between 10 and 90 percent. With these bounds, the use of LIST-coated catheters could save between $874 million and $7.9 billion in the U.S., and $686 million and $6.2 billion in the E.U., and between $1.6 billion and $14.1 billion in both markets

combined. The societal analysis supports the hypothesis that LIST coating will results in lower patient morbidity and mortality and lower associated healthcare costs.

We use these findings to evaluate the societal-level cost-effectiveness of LIST-coated catheters, on a per-catheter basis. The adoption of LIST coatings will increase the unit catheter price, but these costs are forecast to be offset by reduced morbidity and mortality and reduced healthcare costs. Assuming a 20 percent price increase, the adoption of LIST-coated catheters would increase the per catheter cost by $44 in the U.S. and $10 in the E.U. This is well offset by the cost savings in terms of reduced morbidity, mortality, and healthcare costs, which would be $213 to $914 per catheter in the U.S. and $68 to $514 per catheter in the E.U. These data support the hypothesis that adopting LIST-coated catheters would result in lowered patient morbidity and mortality and lower medical costs.

The firm-level analysis considers three scenarios which either increase market share by 20 percent, increase the unit catheter price by 74 percent, or both, and considers both the U.S. and E.U. markets. A firm gaining a 20 percent increase in market share would see increased revenues of $15.6 million per year. A firm gaining a 74 percent price increase in catheter sales would see increased revenues of $57.8 million per year. A firm that realizes both a market share increase of 20 percent and a price increase of 74 percent by implementing LIS-coated catheters would see increased revenues of $73.4 million per year. These data indicate that a firm should attempt to increase both the market share and price charged per catheter, or if only one avenue can be pursued, then a price increase leads to greater profits.

Challenges and Limitations of the Study

There are several limitations of this study and its approach. First, this case study utilizes a relatively simple model of the process of developing, marketing, and adopting a new medical device, which may not fully capture the complexity of this process. Every effort has been made to include all critical parameters, but the variables selected for inclusion in the model are subject to the author's selection bias.

Second, the results of this study can only be as valid as the inputs used. The data sources are the most current available in published literature and market reports, but with data on CRBIs in particular, there are problems collecting and reporting the data. In addition to the basic problem of estimating which infections are associated with catheter use and which would have happened anyway, there are differences in reporting requirements between hospitals and geographic regions.

Third, because LIST-coated catheters haven't been developed yet, this study must use numerous assumptions. For the societal analysis, these are centered on how much LIST-coated catheters would reduce CRBSIs. If the use of LIST-coated catheters does not provide the expected medical treatment cost savings, the per catheter savings could be substantially lower or non-existent. For the firm-level analysis, the assumptions that a firm could capture an additional 20 percent of the CVC market or increase prices by 74 percent may not be valid. For example, it may be difficult for large, mature, consolidated companies such as catheter manufacturing firms to capture large gains in market share, and there is a chance that the market will not bear the assumed price increase for the LIST-coated catheter. Additionally, the specific development costs for LIST-coated catheters are assumed to be included in the firm's general research and development budget, and are outside the scope of this study.

Finally, this study is a forecast based on current market conditions reported in the literature, and this case study cannot fully anticipate technological or other changes that affect either the probability of infection or the costs of the outcomes modeled in this case study. Even small changes in the cost of medical treatment or probability of developing infection may result in large discrepancies in the relative expected value of LIST-coated catheters. For instance, there are ongoing efforts to educate healthcare providers on proper hygiene and technique when inserting catheters. If these efforts were to be successful, the lower baseline incidence of CRBSIs may reduce the expected value of using LIST-coated catheters. Similarly, unanticipated disruptive technological changes, such as other firms developing similar technologies that lower the baseline incidence or treatment cost for CRBSI, would make LIST catheters a less valuable proposition.

Further Implications of the Study

This research predicts that there is potential for large societal and economic benefits from adopting LIST-coated catheters, and these benefits may extend to other medical devices. LIST-coatings are a platform technology, that can be optimized for many disparate applications. Many medical devices are made of metal or polymers that could be treated with LIST-coatings and are subject to biofouling and the potential for infections.

Medical devices such as prosthetics, surgical tools, sensors, and medical implants, are subject to biofouling when exposed to blood and other body fluids. Biofouling often leads to infections requiring the equipment to be replaced and the patient to be treated with antibiotics (Damodaran, 2016). These device-associated-

infections account for 25.6 percent of health care associated infections (Magill, 2014). While antibiotics can address some of these infections, the widespread use of antibiotics may lead to antibiotic resistance.

LIST-coating may help prevent infections from occurring in the first place, and (as seen in this case study), the high human and financial cost of healthcare-acquired infections mean that there are great societal and firm-level benefits to be had from developing these applications.

Appendix 1.

Tables

Table 6: Central Venous Catheter Market

	Estimate 1	Estimate 2	Estimate 3	Average	Sources
U.S.					
Number Central Venous Catheters Used per Year	5,000,000	4,000,000	3,000,000	**4,000,000**	McGee, 2003; Frasca, 2010; Joint Commission, 2012
Central Venous Catheter Market Size	$295,000,000	$225,000,000	$194,000,000	**$238.0 M**	Future Market Insights, 2016b; ASD Reports, 2012
Calculated Standard Catheter Cost	$59	$56	$65	**$60**	McGee, 2003; Frasca, 2010; Joint Commission, 2012; Future Market Insights, 2016b; ASD Reports, 2012
E.U.					
Number Central Venous Catheters Used per Year	11,600,000	9,200,000	6,900,000	**9.2 M**	McGee, 2003; Frasca, 2010; Joint Commission, 2012
Central Venous Catheter Market Size	$117,000,000	$117,000,000	$117,000,000	**$117.0 M**	Future Market Insights, 2016b; Future Market Insights, 2016a
Calculated Standard Catheter Cost	$10	$13	$17	**$13**	McGee, 2003; Frasca, 2010; Joint Commission, 2012; Future Market Insights, 2016b; Future Market Insights, 2016a

Table 7: Health Outcome Probabilities

	Estimate 1	Estimate 2	Estimate 3	Average	Sources
U.S.					
Health, Including Biofilm with No CRBSI					
Health	95%	95%	97%	**96%**	McGee, 2010; Frasca, 2010; Joint Commission, 2012, Tacconelli, 2009
Non-Biofilm or Biofilm-Associated CRBSI	5%	5%	3%	**4%**	McGee, 2010; Frasca, 2010; Joint Commission, 2012, Tacconelli, 2009
Non-Biofilm vs Biofilm Associated CRBSI					
Non-Biofilm-Associated CRBSI	60%	73%	82%	**72%**	Gahlot, 2014; Hu, 2004
Biofilm-Associated CRBSI	40%	27%	18%	**28%**	Gahlot, 2014; Hu, 2004
Non-biofilm-associated CRBSI Health Outcomes					
CRBSI-Associated Morbidity	90%	88%	75%	**84%**	Joint Commission, 2012; Gahlot, 2014; AHRQ, 2001
CRBSI-Associated Mortality	10%	12%	25%	**16%**	Joint Commission, 2012; Gahlot, 2014; AHRQ, 2001
Biofilm-Associated CRBSI Health Outcomes					
Biofilm-Associated Morbidity	90%	88%	75%	**84%**	Joint Commission, 2012; Gahlot, 2014; AHRQ, 2001
Biofilm-Associated Mortality	10%	12%	25%	**16%**	Joint Commission, 2012; Gahlot, 2014; AHRQ, 2001
E.U.					
Health, Including Biofilm with No CRBSI					
Health	95%	96%	97%	**96%**	McGee, 2010; Frasca, 2010; Joint Commission, 2012; ECDC, 2013
Non-Biofilm or Biofilm-Associated CRBSI	5%	4%	3%	**4%**	McGee, 2010; Frasca, 2010; Joint Commission, 2012; ECDC, 2013
Non-Biofilm vs Biofilm Associated CRBSI					
Non-biofilm-Associated CRBSI	50%	60%	70%	**60%**	Gahlot, 2014; Hu, 2004
Biofilm-Associated CRBSI	50%	40%	30%	**40%**	Gahlot, 2014; Hu, 2004
Non-Biofilm-Associated CRBSI Health Outcomes					
CRBSI-Associated Morbidity	89%	87%	82%	**86%**	Tacconelli, 2009
CRBSI-Associated Mortality	11%	13%	18%	**14%**	Tacconelli, 2009
Biofilm-Associated CRBSI Health Outcomes					
Biofilm-Associated Morbidity	89%	87%	82%	**86%**	Tacconelli, 2009
Biofilm-Associated Mortality	11%	13%	18%	**14%**	Tacconelli, 2009

Table 8: Number of Cases of CRBSIs

	Estimate 1	Estimate 2	Estimate 3	Average	Sources
U.S.					
Total Catheters					
Total Catheters	5,000,000	4,000,000	3,000,000	**4,000,000**	McGee, 2003; Frasca, 2010; Joint Commission, 2012
Health					
Health	4,750,000	3,796,000	2,916,000	**3,820,667**	McGee, 2003; Frasca, 2010; Joint Commission, 2012, Tacconelli, 2009
Non-Biofilm-Associated CRBSI					
CRBSI-Associated Morbidity	135,000	130,603	51,660	**108,259**	Joint Commission, 2012; Gahlot, 2014; AHRQ, 2001; Hu, 2004
CRBSI-Associated Mortality	15,000	18,317	17,220	**20,264**	Joint Commission, 2012; Gahlot, 2014; AHRQ, 2001; Hu, 2004
Biofilm-Associated Morbidity	90,000	48,305	11,340	**42,800**	Joint Commission, 2012; Gahlot, 2014; AHRQ, 2001
Biofilm-Associated Mortality	10,000	6,775	3,780	**8,011**	Joint Commission, 2012; Gahlot, 2014; AHRQ, 2001
E.U.					
Total Catheters					
Total Catheters	11,558,805	9,247,044	6,935,283	**9,247,044**	McGee, 2003; Frasca, 2010; Joint Commission, 2012
Health					
Health	11,002,805	8,905,044	6,731,983	**8,879,944**	McGee, 2010; Frasca, 2010; Joint Commission, 2012; ECDC, 2013
Non-biofilm-associated CRBSI					
CRBSI-Associated Morbidity	247,420	178,524	116,694	**189,424**	Gahlot, 2014; Tacconelli, 2009; ECDC, 2013; Hu, 2004
CRBSI-Associated Mortality	30,580	26,676	25,616	**30,836**	Gahlot, 2014; Tacconelli, 2009; ECDC, 2013; Hu, 2004
Biofilm					
Biofilm-Associated Morbidity	247,420	119,016	50,012	**126,282**	Gahlot, 2014; Tacconelli, 2009; ECDC, 2013; Hu, 2004
Biofilm-Associated Mortality	30,580	17,784	10,978	**20,558**	Gahlot, 2014; Tacconelli, 2009; ECDC, 2013; Hu, 2004

Table 9. Unit Costs Associated with Catheter Use, Morbidity, and Mortality.

	Estimate 1	Estimate 2	Estimate 3	Average	Sources
U.S.					
Unit Costs per Patient					
Procedure Cost Catheter Insertions	$2,052	$1,032	$868	**$1,317**	Bard, 2010
Morbidity Treatment Cost	$65,000	$46,000	$31,000	**$47,333**	Zimlichman, 2013
Mortality Valuation	$10,000,000	$8,000,000	$6,000,000	**$8,000,000**	Doucouliagos, 2014
Mortality Directly Attributable to CRBSI	0.8%	0.6%	0.4%	**0.6%**	Hu, 2004
Value of Mortality Directly Attributable to CRBSI	$80,000	$48,000	$24,000	**$48,000**	Doucouliagos, 2014; Hu, 2004
Average Cost per Patient					
Health	$2,052	$1,032	$868	**$1,317**	Bard, 2010
Morbidity	$67,052	$47,032	$31,868	**$48,651**	Zimlichman, 2013; Bard, 2010
Mortality	$82,052	$49,032	$24,868	**$49,317**	Doucouliagos, 2014, Bard, 2010
E.U.					
Unit Costs per Patient					
Procedure Cost	$1,481	$1,460	$1,368	**$1,436**	Biffi, 2014
Morbidity Treatment Cost	$25,000	$15,000	$12,000	**$17,333**	Gahlot, 2014; Tacconelli, 2009; ECDC, 2013; Hu, 2004
Mortality Valuation	$4,172,479	$2,781,652	$1,390,827	**$2,781,653**	WHO, 2014
Mortality Directly Attributable to CRBSI	0.8%	0.6%	0.4%	**0.6%**	Hu, 2004
Value of Mortality Directly Attributable to CRBSI	$33,380	$16,690	$5,563	**$16,690**	WHO, 2014; Hu, 2004
Average Cost per Patient					
Health	$1,481	$1,460	$1,368	**$1,436**	Biffi, 2014
Morbidity	$26,481	$16,460	$13,368	**$18,770**	Gahlot, 2014; Tacconelli, 2009; ECDC, 2013; Hu, 2004, Biffi, 2014
Mortality	$34,861	$18,150	$6,931	**$18,126**	WHO, 2014; Biffi, 2014

Table 10: Costs for Treating CRBSIs

	Number of Cases	Average Cost Per Patient	Aggregate Costs	Sources
U.S.				
Health				
Health	3,820,667	$1,317	$5,033,091,556	McGee, 2003; Frasca, 2010; Joint Commission, 2012, Tacconelli, 2009; Bard, 2010
Non-Biofilm-Associated CRBSI				
CRBSI-Associated Morbidity	108,259	$48,651	$5,266,850,720	Joint Commission, 2012; Gahlot, 2014; AHRQ, 2001; Hu, 2004; Zimlichman, 2013; Bard, 2010
CRBSI-Associated Mortality	20,264	$49,317	$999,350,186	Joint Commission, 2012; Gahlot, 2014; AHRQ, 2001; Hu, 2004; Doucouliagos, 2014, Bard, 2010
Biofilm				
Biofilm-Associated Morbidity	42,800	$48,651	$2,082,243,308	Joint Commission, 2012; Gahlot, 2014; AHRQ, 2001; Zimlichman, 2013; Bard, 2010
Biofilm-Associated Mortality	8,011	$49,317	$395,091,934	Joint Commission, 2012; Gahlot, 2014; AHRQ, 2001; Doucouliagos, 2014, Bard, 2010
E.U.				
Health				
Health	8,879,944	$1,436	$12,754,559,826	McGee, 2010; Frasca, 2010; Joint Commission, 2012; ECDC, 2013; Biffi, 2014
Non-Biofilm-Associated CRBSI				
CRBSI-Associated Morbidity	189,424	$18,770	$3,555,417,831	Gahlot, 2014; Tacconelli, 2009; ECDC, 2013; Hu, 2004; Biffi, 2014
CRBSI-Associated Mortality	30,836	$18,126	$558,948,275	Gahlot, 2014; Tacconelli, 2009; ECDC, 2013; Hu, 2004; WHO, 2014; Biffi, 2014
Biofilm				
Biofilm-Associated Morbidity	126,282	$18,770	$2,370,278,554	Gahlot, 2014; Tacconelli, 2009; ECDC, 2013; Hu, 2004; Gahlot Biffi, 2014
Biofilm-Associated Mortality	20,558	$18,126	$372,632,183	Gahlot, 2014; Tacconelli, 2009; ECDC, 2013; Hu, 2004; WHO, 2014; Biffi, 2014

Table 11 : Reduction in Morbidity and Mortality from Adopting LIST-coated Catheters

	Baseline Cases/Costs	10% Reduction Difference from Baseline	90% Reduction Difference from Baseline
U.S.			
Morbidity Incidence	151,058	-135,953	-15,106
Mortality Incidence	28,275	-25,447	-2,827
Morbidity Cost Savings	$7,349,094,028	-$6,614,184,625	-$734,909,403
Mortality Cost Savings	$1,394,442,120	-$1,254,997,908	-$139,444,212
Total Cost Savings	$8,743,536,148	-$7,869,182,533	-$874,353,615
E.U.			
Morbidity Incidence	315,706	-284,135	-31,571
Mortality Incidence	51,394	-46,255	-5,139
Morbidity Cost Savings	$5,925,696,385	-$5,333,126,746	-$592,569,638
Mortality Cost Savings	$931,580,458	-$838,422,412	-$93,158,046
Total Cost Savings	$6,857,276,843	-$6,171,549,159	-$685,727,684
Total Combined			
Morbidity Incidence	466,764	-420,088	-46,676
Mortality Incidence	79,669	-71,702	-7,967
Morbidity Cost Savings	$13,274,790,413	-$11,947,311,371	-$1,327,479,041
Mortality Cost Savings	$2,326,022,579	-$2,093,420,321	-$232,602,258
Total Cost Savings	$15,600,812,991	-$14,040,731,692	-$1,560,081,299

Table 12: Treatment Costs: Traditional Catheters

	Number of Cases	Average Cost Per Patient	Aggregate Costs	Infection-Related Cost per Patient	Aggregate Infection-Related Cost	Sources
U.S.						
Health						
Health	3,820,667	$1,317	$5,033,091,556	$0	$0	McGee, 2003; Frasca, 2010; Joint Commission, 2012, Tacconelli, 2009; Bard, 2010
Non-Biofilm-Associated CRBSI						
CRBSI-Associated Morbidity	108,259	$48,651	$5,266,850,720	$47,333	$5,124,238,121	Joint Commission, 2012; Gahlot, 2014; AHRQ, 2001; Hu, 2004; Zimlichman, 2013; Bard, 2010
CRBSI-Associated Mortality	20,264	$49,317	$999,350,186	$48,000	$972,656,178	Joint Commission, 2012; Gahlot, 2014; AHRQ, 2001; Hu, 2004; Doucouliagos, 2014, Bard, 2010
Biofilm						
Biofilm-Associated Morbidity	42,800	$48,651	$2,082,243,308	$47,333	$2,025,861,583	Joint Commission, 2012; Gahlot, 2014; AHRQ, 2001; Zimlichman, 2013; Bard, 2010
Biofilm-Associated Mortality	8,011	$49,317	$395,091,934	$48,000	$384,538,489	Joint Commission, 2012; Gahlot, 2014; AHRQ, 2001; Doucouliagos, 2014, Bard, 2010
Total U.S.						
Total U.S.	4,000,000	$3,444	$13,776,627,704	$2,126.82	$8,507,294,370	Calculation
E.U.						
Health						
Health	8,879,944	$1,436	$12,754,559,826	$0	$0	McGee, 2010; Frasca, 2010; Joint Commission, 2012; ECDC, 2013; Biffi, 2014
Non-Biofilm-Associated CRBSI						
CRBSI-Associated Morbidity	189,424	$18,770	$3,555,417,831	$17,333	$3,283,342,400	Gahlot, 2014; Tacconelli, 2009; ECDC, 2013; Hu, 2004; Biffi, 2014
CRBSI-Associated Mortality	30,836	$18,126	$558,948,275	$16,690	$514,656,926	Gahlot, 2014; Tacconelli, 2009; ECDC, 2013; Hu, 2004; WHO, 2017; Biffi, 2014
Biofilm						
Biofilm-Associated Morbidity	126,282	$18,770	$2,370,278,554	$17,333	$2,188,894,933	Gahlot, 2014; Tacconelli, 2009; ECDC, 2013; Hu, 2004; Gahlot Biffi, 2014
Biofilm-Associated Mortality	20,558	$18,126	$372,632,183	$16,690	$343,104,617	Gahlot, 2014; Tacconelli, 2009; ECDC, 2013; Hu, 2004; WHO, 2017; Biffi, 2014
Total E.U.						
Total E.U.	9,247,044	$2,121	$19,611,836,669	$685	$6,329,998,876	Calculation
Total Combined						
Total Combined	13,247,044	$2,520	$33,388,464,373	$1,120	$14,837,293,247	Calculation

Table 13: Treatment Costs: LIST-coated Catheter 10 Percent Scenario

	Number of Cases	Average Cost Per Patient	Aggregate Costs	Infection-Related Cost per Patient	Aggregate Infection-Related Cost	Sources
U.S.						
Health						
Health	3,838,600	$1,362	$5,227,070,669	$0	$0	McGee, 2003; Frasca, 2010; Joint Commission, 2012, Tacconelli, 2009; Bard, 2010
Non-Biofilm-Associated CRBSI						
CRBSI-Associated Morbidity	97,433	$48,695	$4,744,489,657	$47,333	$4,611,814,309	Joint Commission, 2012; Gahlot, 2014; AHRQ, 2001; Hu, 2004; Zimlichman, 2013; Bard, 2010
CRBSI-Associated Mortality	18,237	$49,362	$900,224,529	$48,000	$875,390,560	Joint Commission, 2012; Gahlot, 2014; AHRQ, 2001; Hu, 2004; Doucouliagos, 2014, Bard, 2010
Biofilm						
Biofilm-Associated Morbidity	38,520	$48,695	$1,875,728,469	$47,333	$1,823,275,424	Joint Commission, 2012; Gahlot, 2014; AHRQ, 2001; Zimlichman, 2013; Bard, 2010
Biofilm-Associated Mortality	7,210	$49,362	$355,902,721	$48,000	$346,084,640	Joint Commission, 2012; Gahlot, 2014; AHRQ, 2001; Doucouliagos, 2014, Bard, 2010
Total U.S.						
Total U.S.	4,000,000	$3,276	$13,103,416,044	$1,914	$7,656,564,933	Calculation
E.U.						
Health						
Health	8,916,654	$1,446	$12,894,484,698	$0	$0	McGee, 2010; Frasca, 2010; Joint Commission, 2012; ECDC, 2013; Biffi, 2014
Non-Biofilm-Associated CRBSI						
CRBSI-Associated Morbidity	170,481	$18,779	$3,201,543,205	$17,333	$2,955,008,160	Gahlot, 2014; Tacconelli, 2009; ECDC, 2013; Hu, 2004; Biffi, 2014
CRBSI-Associated Mortality	27,753	$18,136	$503,324,845	$16,690	$463,191,233	Gahlot, 2014; Tacconelli, 2009; ECDC, 2013; Hu, 2004; WHO, 2017; Biffi, 2014
Biofilm						
Biofilm-Associated Morbidity	113,654	$18,779	$2,134,362,137	$17,333	$1,970,005,440	Gahlot, 2014; Tacconelli, 2009; ECDC, 2013; Hu, 2004; Gahlot Biffi, 2014
Biofilm-Associated Mortality	18,502	$18,136	$335,549,897	$16,690	$308,794,155	Gahlot, 2014; Tacconelli, 2009; ECDC, 2013; Hu, 2004; WHO, 2017; Biffi, 2014
Total E.U.						
Total E.U.	9,247,044	$2,062	$19,069,264,782	$616	$5,696,998,989	Calculation
Total Combined						
Total Combined	13,247,044	$2,429	$32,172,680,826	$1,008	$13,353,563,922	Calculation

Table 14: Treatment Costs: LIST-coated Catheter 90 Percent Scenario

	Number of Cases	Average Cost Per Patient	Aggregate Costs	Infection-Related Cost per Patient	Aggregate Infection-Related Cost	Sources
U.S.						
Health						
Health	3,982,067	$1,362	$5,422,431,062	$0	$0	McGee, 2003; Frasca, 2010; Joint Commission, 2012, Tacconelli, 2009; Bard, 2010
Non-Biofilm-ssociated CRBSI						
CRBSI-Associated Morbidity	10,826	$48,695	$527,165,517	$47,333	$512,423,812	Joint Commission, 2012; Gahlot, 2014; AHRQ, 2001; Hu, 2004; Zimlichman, 2013; Bard, 2010
CRBSI-Associated Mortality	2,026	$49,362	$100,024,948	$48,000	$97,265,618	Joint Commission, 2012; Gahlot, 2014; AHRQ, 2001; Hu, 2004; Doucouliagos, 2014, Bard, 2010
Biofilm						
Biofilm-Associated Morbidity	4,280	$48,695	$208,414,274	$47,333	$202,586,158	Joint Commission, 2012; Gahlot, 2014; AHRQ, 2001; Zimlichman, 2013; Bard, 2010
Biofilm-Associated Mortality	801	$49,362	$39,544,747	$48,000	$38,453,849	Joint Commission, 2012; Gahlot, 2014; AHRQ, 2001; Doucouliagos, 2014, Bard, 2010
Total U.S.						
Total U.S.	4,000,000	$1,574	$6,297,580,548	$213	$850,729,437	Calculation
E.U.						
Health						
Health	9,210,334	$1,446	$13,319,179,005	$84	$777,349,262	McGee, 2010; Frasca, 2010; Joint Commission, 2012; ECDC, 2013; Biffi, 2014
Non-Biofilm-Associated CRBSI						
CRBSI-Associated Morbidity	18,942	$18,779	$355,727,023	$17,418	$329,932,969	Gahlot, 2014; Tacconelli, 2009; ECDC, 2013; Hu, 2004; Biffi, 2014
CRBSI-Associated Mortality	3,084	$18,136	$55,924,983	$16,774	$51,725,951	Gahlot, 2014; Tacconelli, 2009; ECDC, 2013; Hu, 2004; WHO, 2017; Biffi, 2014
Biofilm						
Biofilm-Associated Morbidity	12,628	$18,779	$237,151,349	$17,418	$219,955,313	Gahlot, 2014; Tacconelli, 2009; ECDC, 2013; Hu, 2004; Gahlot Biffi, 2014
Biofilm-Associated Mortality	2,056	$18,136	$37,283,322	$16,774	$34,483,967	Gahlot, 2014; Tacconelli, 2009; ECDC, 2013; Hu, 2004; WHO, 2017; Biffi, 2014
Total E.U.						
Total E.U.	9,247,044	$1,515	$14,005,265,681	$153	$1,413,447,462	Calculation
Total Combined						
Total Combined	13,247,044	$1,533	$20,302,846,229	$171	$2,264,176,899	Calculation

References

AHRQ. (2001). Making Healthcare Safer: A Critical Analysis of Patient Safety Practices. Retrieved from https://archive.ahrq.gov/clinic/ptsafety/chap16a.htm (Accessed March 12, 2017).

ASD Reports. (2012, January 31). Global Central Venous Catheters Market was Valued $582.2m in 2010. Retrieved from https://www.asdreports.com/news-193/global-central-venous-catheters-market-was-valued-5822m-2010 (Accessed August 2, 2017).

Bard Access Systems. (2010). Required HCPS Reimbursement Coding. Retrieved from http://www.veins4life.com/downloads/pdf/VFL_Flash_ReimbursR5.pdf (Accessed July 15, 2017).

Barthlott, W., Neinhuis, C. (1997). Purity of the sacred lotus, or escape from contamination in biological surfaces. Planta, 202(1), 1-8.

Boston Consulting Group. (2012, June). Regulation and Access to Innovative Medical Technologies A comparison of the FDA and EU Approval Processes and their Impact on Patients and Industry. Retrieved from http://www.medtecheurope.org/sites/default/files/resource_items/files/01062012_BCG_Regulation%20and%20Access%20to%20Innovative%20Medical%20Technologies_Backgrounder.pdf (Accessed April 1, 2017).

BSI Group. (2010). CE marking The fast route to compliance in the European Union. Retrieved from https://www.bsigroup.com/Documents/product-certification/BSI-CE-marking-brochure-UK-EN.pdf (Accessed August 2, 2017).

Buntz, B. The Rise of Medtech. (2011, June 10). Retrieved from http://www.mddionline.com/article/rise-medtech (Accessed January 1, 2017).

Bureau of Economic Analysis (BEA). (2017). Table 1.1.9. Implicit Price Deflators for Gross Domestic Product. Retrieved from https://www.bea.gov/iTable/iTableHtml.cfm?reqid=19&step=3&isuri=1&1910=x&0=-99&1921=survey&1903=13&1904=1998&1905=2017&1906=a&1911=0 (Accessed February 4, 2018).

Centers for Disease Control and Prevention (CDC). (2011). Guidelines for the prevention of intravascular cardiac related infections, 2011. Retrieved from https://www.cdc.gov/hai/pdfs/bsi-guidelines-2011.pdf (Accessed January 1, 2017).

Costerton, J. W., Lewandowski, Z., Caldwell, D. E., Korber, D. R., Lappin-Scott, H. M. (1995). Microbial biofilms. Annual Reviews in Microbiology, 49(1), 711-745.

Damodaran, V. B., & Murthy, N. S. (2016). Bio-inspired strategies for designing antifouling biomaterials. Biomaterials research, 20(1), 18.

Doucouliagos, H., Stanley, T. D., & Viscusi, W. K. (2014). Publication selection and the income elasticity of the value of a statistical life. Journal of health economics, 33, 67-75.

European Centre for Disease Prevention and Control (ECDC). (2013). Point prevalence survey of healthcare-associated infections and antimicrobial use in European acute care hospitals 2011–2012. Retrieved from http://ecdc.europa.eu/en/publications/Publications/healthcare-associated-infections-antimicrobial-use-PPS.pdf

Food and Drug Administration. (1995, March). Guidance on premarket Notification[510(K)] submissions for short-term and long-term intravascular catheters. Retrieved from https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm080766.pdf

Francolini, I., & Donelli, G. (2010). Prevention and control of biofilm-based medical-device-related infections. FEMS Immunology & Medical Microbiology, 59(3), 227-238.

Frasca, D., Dahyot-Fizelier, C., & Mimoz, O. (2010). Prevention of central venous catheter-related infection in the intensive care unit. Critical Care, 14(2), 1.

Future Market Insights. (2016a, November 8). Global Central Venous Catheter Market Anticipated to be Valued at US$ 1,108.4 Mn by 2026. Retrieved from http://www.futuremarketinsights.com/press-release/central-venous-catheter-market (Accessed August 1, 2017).

Future Market Insights. (2016b, November 8). Central Venous Catheter Market: Non-tunnelled Catheters Expected to Dominate the Market Through 2026: Global IndustryAnalysis and Opportunity Assessment, 2016-2026. Retrieved from https://www.futuremarketinsights.com/reports/central-venous-catheter-market (Accessed August 1, 2017).

Gahlot, R., Nigam, C., Kumar, V., Yadav, G., & Anupurba, S. (2014). Catheter-related bloodstream infections. International journal of critical illness and injury science, 4(2), 162.

Harron, K., Mok, Q., Hughes, D., Muller-Pebody, B., Parslow, R., Ramnarayan, P., & Gilbert, R. (2016). Generalisability and cost-impact of antibiotic-impregnated central venous catheters for reducing risk of bloodstream infection in paediatric intensive care units in England. PloS one, 11(3), e0151348.

Howell, C., Vu, T. L., Lin, J. J., Kolle, S., Juthani, N., Watson, E., Aizenberg, J. (2014). Self-replenishing vascularized fouling-release surfaces. ACS applied materials & interfaces, 6(15), 13299-13307.

Hu, K. K., Veenstra, D. L., Lipsky, B. A., & Saint, S. (2004). Use of maximal sterile barriers during central venous catheter insertion: clinical and economic outcomes. Clinical infectious diseases, 39(10), 1441-1445.

Hughes, R. (Ed.). (2008). Patient safety and quality: An evidence-based handbook for nurses (Vol. 3). Rockville, MD: Agency for Healthcare Research and Quality.

Joint Commission. (2012). Preventing central line–associated bloodstream infections: a global challenge, a global perspective. Oak Brook, IL: Joint Commission Resources, 4.

Knetsch, M. L., & Koole, L. H. (2011). New strategies in the development of antimicrobial coatings: the example of increasing usage of silver and silver nanoparticles. Polymers, 3(1), 340-366.

Kramer, D. B., Xu, S., & Kesselheim, A. S. (2012). Regulation of medical devices in the United States and European Union.

Leslie, D. C., Waterhouse, A., Berthet, J. B., Valentin, T. M., Watters, A. L., Jain, A., Super, E. H. (2014). A bioinspired omniphobic surface coating on medical devices prevents thrombosis and biofouling. Nature biotechnology, 32(11), 1134-1140.

MacCallum, N., Howell, C., Kim, P., Sun, D., Friedlander, R., Ranisau, J., Wong, T. S. (2014). Liquid-infused silicone as a biofouling-free medical material. ACS Biomaterials Science & Engineering, 1(1), 43-51.

Magill, S. S., Edwards, J. R., Bamberg, W., Beldavs, Z. G., Dumyati, G., Kainer, M. A., ... & Ray, S. M. (2014). Multistate point-prevalence survey of health care–associated infections. New England Journal of Medicine, 370(13), 1198-1208.

McGee, D. C., & Gould, M. K. (2003). Preventing complications of central venous catheterization. New England Journal of Medicine, 348(12), 1123-1133.

Medical Device and Diagnostic Industry (MDDI). (2010). So many polymers, so little time. Retrieved from http://www.mddionline.com/article/so-many-polymers-so-little-time (Accessed January 1, 2017).

Maki, D. G., & Ringer, M. (1991). Risk Factors for Infusion-related Phlebitis with Small Peripheral Venous CathetersA Randomized Controlled Trial. Annals of internal medicine, 114(10), 845-854.

Makower, J., Meer, A., & Denend, L. (2010). FDA impact on US medical technology innovation: a survey of over 200 medical technology companies. Advanced

Medical Technology Association, Washington, DC, Retrieved from: http://www. advamed. org/NR/rdonlyres/040E6C33-380B-4F6B-AB58-9AB1C0A7A3CF/0/makowerreportfinal. pdf.

Medical Device and Diagnostic Industry (MDDI). (2013). New extrusion techniques advance catheter design. Retrieved from http://www.mddionline.com/article/new-extrusion-techniques-advance-catheter-design (Accessed January 1, 2017).

Mermel, L. A. (2000). Prevention of central venous catheter related infection. Annals of internal medicine, 132(5), 391-402.

Quéré, D. (2005). Non-sticking drops. *Reports on Progress in Physics*, *68*(11), 2495.

Quéré, D. (2008). Wetting and roughness. *Annu. Rev. Mater. Res.*, *38*, 71-99.

Rivera, A. M., Strauss, K. W., Van Zundert, A., & Mortier, E. (2005). The history of peripheral intravenous catheters: how little plastic tubes revolutionized medicine. Acta Anæsthesiologica Belgica, 56(3), 271.

Ryder, H. F., McDonough, C. M., Tosteson, A. N., & Lurie, J. D. (2009, December). Decision analysis and cost-effectiveness analysis. In Seminars in spine surgery (Vol. 21, No. 4, pp. 216-222).

Scott, R. D. (2009). The direct medical costs of healthcare-associated infections in US hospitals and the benefits of prevention. Division of Healthcare Quality Promotion National Center for Preparedness, Detection, and Control of Infectious Diseases, Centers for Disease Control and Prevention.

Shah, H., Bosch, W., Thompson, K. M., & Hellinger, W. C. (2013). Intravascular catheter-related bloodstream infection. The Neurohospitalist, 3(3), 144-151.

Sheth, N. K., Franson, T. R., Rose, H. D., Buckmire, F. L., Cooper, J. A., & Sohnle, P. G. (1983). Colonization of bacteria on polyvinyl chloride and Teflon intravascular catheters in hospitalized patients. Journal of clinical microbiology, 18(5), 1061-1063.

Smith, J. D., Dhiman, R., Anand, S., Reza-Garduno, E., Cohen, R. E., McKinley, G. H., & Varanasi, K. K. (2013). Droplet mobility on lubricant-impregnated surfaces. Soft Matter, 9(6), 1772-1780.

Snowbeck, C. (2008, May 20). Medtronics get 4Q Lift from new stent. Twin Cities Pioneer Press. Retrieved from http://www.twincities.com/2008/05/20/medtronic-gets-4q-lift-from-new-stent (Accessed February 10, 2017).

Sousa, C., Henriques, M., & Oliveira, R. (2011). Mini-review: antimicrobial central venous catheters–recent advances and strategies. Biofouling, 27(6), 609-620.

Tacconelli, E., Smith, G., Hieke, K., Lafuma, A., & Bastide, P. (2009). Epidemiology, medical outcomes and costs of catheter-related bloodstream infections in intensive care units of four European countries: literature-and registry-based estimates. Journal of Hospital Infection, 72(2), 97-103.

Treter, J., & Macedo, A. J. (2011). Catheters: a suitable surface for biofilm formation. Handbook: science against microbial pathogens: communicating current research and technological advances. Spain: Formatex Research Center, 835-842.

Veenstra, D. L., Saint, S., & Sullivan, S. D. (1999). Cost-effectiveness of antiseptic-impregnated central venous catheters for the prevention of catheter-related bloodstream infection. *Jama*, *282*(6), 554-560.

World Health Organization (WHO). (2014) Value of Statistical Life. Retrieved from http://heatwalkingcycling.org/index.php?pg=requirements&act=vsl (Accessed May, 12, 2017).

Zaharoff, H. (2012). Setting values and royalty rates for medical and life sciences businesses. Retrieved from http://www.mbbp.com/news/setting-values-and-royalty-rates#footnotes (Accessed March 3, 2017)

Zimlichman, E., Henderson, D., Tamir, O., Franz, C., Song, P., Yamin, C. K., Bates, D. W. (2013). Health care–associated infections: a meta-analysis of costs and financial impact on the US health care system. JAMA internal medicine, 173(22), 2039-2046.