Commercialization of contact-free blood pressure monitoring technology

By

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Dedicated to my Parents for their love and encouragement!
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Abstract

by

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This thesis will provide a commercialization strategy for a contact-free blood pressure monitoring application with an overview of the circulatory system, blood pressure, pathological conditions affecting blood pressure and the technology platform of the application. The EarlySense patient supervision system, EverOn™, comprises a contact-free sensor and a bedside unit that currently displays the patient’s heart rate, respiratory rate and body motion. The company intends to incorporate the additional functionality of contact-free blood pressure monitoring. Upon detection of a fluctuation in blood pressure, EverOn will alert care providers by activating an alarm. The additional functionality will allow the company to expand into new markets and to effectively predict patient deterioration. The EverOn device has received FDA 510(k) clearance, is CE approved and has demonstrated successful clinical trials. EverOn’s initial target market comprises general medical wards in hospitals. Future markets include home care and long term care markets.
1. Introduction

1.1. Internship at BioEnterprise

I joined BioEnterprise in January 2009 as a Business Analyst and have been involved in conducting market research, preparing initial reviews and due diligence summaries for early stage medical device and therapeutics companies. I have also been very active in the area of grant writing and have played significant roles in a National Science Foundation (NSF) grant and a commercialization grant for the Global Cardiovascular Innovation Center (GCIC). The GCIC grant was written on behalf of EarlySense to secure funding for the introduction of the blood pressure monitoring application into their EverOn device. The company received funding of $441,000 to investigate the incorporation of a noninvasive contact-free blood pressure application into their device.

1.2. EarlySense overview

EarlySense is an Israel based company founded in 2004 by CEO, Avner Halperin. The company has a multidisciplinary team of 25 employees coordinating between clinical, research and development, and marketing areas. EarlySense has developed a proprietary, contact-free, intelligent patient supervision system, EverOn™, that is intended for use in the hospital, long term care and home care markets. The EverOn system is FDA cleared in the U.S. and has received CE approval in Europe. The company continues to develop clinical study-based evidence to support its value to
the healthcare system. Their initial product launch is focused on medical-surgical wards in hospitals.

1.3. Scope of thesis

This thesis is a result of my interaction with EarlySense as part of my internship at BioEnterprise. The document provides a commercialization strategy for EarlySense’s contact-free blood pressure application with an overview of the circulatory system, blood pressure, pathology of diseases affecting blood pressure and technology platform of the device. It includes a detailed description of the medical importance of this device, the ‘market-entry’ plan of the company and strategic steps that can be taken for the successful launch of the product. Favorable trends in the market and expected challenges are discussed. An assessment of the business is provided at the end.

2. Technology description

2.1. Scientific background

2.1.1. Overview of the circulatory system

The circulatory system is an organ system that supplies nutrients to the tissues, and transports waste products away from them. It contributes to the regulation of body temperature and pH for homeostasis and distribution of hormones to ensure
normal cell function. The heart, blood and blood vessels are the main components of the circulatory system. The heart is a muscular organ whose function is to pump blood to the cells of the body through the blood vessels. Blood is a body fluid that carries nutrients such as amino acids and electrolytes, gases such as oxygen and carbon dioxide and other metabolic products. It consists of plasma, red blood cells, white blood cells and platelets. Blood vessels are tubular structures that transport blood throughout the body. They can be classified into three major categories: arteries, capillaries and veins. The heart pumps blood into the arteries which transport it to the various tissues. Arteries branch into arterioles and release blood into capillaries. Capillaries facilitate nutrient and fluid exchange. Blood from capillaries is collected by venules which join to form large veins that ultimately return blood to the heart (Ganong 1975) (Guyton and Hall 2003).

Circulation can be divided into pulmonary, systemic and coronary circulations. Pulmonary circulation supplies blood only to the lungs while systemic circulation supplies blood to all other parts of the body. Coronary circulation refers to circulation of blood in the blood vessels of the heart. Coronary arteries supply oxygen rich blood to the myocardium or heart tissue while coronary veins remove the deoxygenated blood from it (Guyton and Hall 2003).
2.1.2. Structure and physiology of the heart

The heart is a hollow muscular organ, enclosed within the pericardium, which is a double walled membrane. An oblique longitudinal septum separates the heart into left and right halves. Each half consists of a posterior receiving chamber, the atrium, and an anterior ejecting chamber, the ventricle. These chambers are externally separated by the coronary sulcus and internally connected by an atrioventricular orifice that allows the unidirectional flow of blood from the atrium to the ventricle. The interatrial septum separates the left and right atria. The atria, mostly the left atrium, form the base of the heart and the left ventricle forms the apex of the heart (Romanes 1981).
Chambers of the heart

As described above, the heart is divided into four chambers – the right and left atria and the right and left ventricles. The right atrium and right ventricle form the right heart while the left atrium and left ventricle form the left heart.

The right heart

The right atrium receives deoxygenated blood from the superior and inferior vena cavae and coronary veins. It then pumps blood into the right ventricle through the tricuspid valve. The right ventricle pumps the received deoxygenated blood to the lungs through the pulmonary artery.

The left heart

The left atrium receives oxygenated blood from four pulmonary veins and pumps it to the left ventricle through the mitral valve, also known as the bicuspid valve or left atrioventricular valve. The left ventricle then pumps oxygenated blood to the aorta which branches to form the systemic circulation (Romanes 1981).

2.1.3. Heart valves

Atrioventricular (A-V) valves

The tricuspid valve between the right atrium and right ventricle, and the mitral valve between the left atrium and left ventricle form the A-V valves. They prevent the backward flow of blood from the ventricles to the atria during ventricular systole. Systole is the period of contraction of the heart when it pumps blood
through the arteries. *Diastole* is the period of relaxation of the heart when it fills with blood.

A-V valves operate passively i.e. they open by a forward pressure gradient and close by a backward pressure gradient. Papillary muscles are attached to the vanes of the A-V valves by means of chordae tendineae. The muscles pull the vanes of the valves toward the ventricles to prevent excess bulging into the atria during ventricular systole. If the chordae tendineae stretch or rupture, the A-V valves may bulge into the atria causing leakage and cardiac inefficiency.

**Semilunar valves**

The aortic valve and the pulmonary valve form the semilunar valves. The aortic valve lies between the left ventricle and the aorta while the pulmonary valve lies between the right ventricle and the pulmonary artery. Semilunar valves prevent the backflow of blood from the arteries into the ventricles during diastole. High arterial pressures cause the valves to close. Rapid closure of valves combined with rapid ejection of blood from the ventricles subject these valves to high mechanical abrasions (Guyton and Hall 2003).
2.1.4. Pumping action of the heart

The ‘Cardiac cycle’ refers to the series of events that occurs from the beginning of one heartbeat to the beginning of the next. The cycle begins with the generation of an action potential in the sinus node. The sinus node is the heart’s natural pacemaker and is located on the right atrium near the opening of the superior vena cava. The action potential then propagates through the atria and then into the ventricles by means of the atrioventricular (AV) node. This is the only point of electrical connection between the atria and the ventricles. Due to the time required for action potential propagation from the right atrium, through the AV node to the ventricles, there is a delay of a fraction of a second during the passage of the potential from the atria to the ventricles. This is an important aspect of cardiac function as it results in the atria acting as primer pumps. They contract ahead of the ventricles and pump blood into them before ventricular contraction begins. Figure 2 below depicts the sequence of electrical and mechanical events that occur during the cardiac cycle (Guyton and Hall 2003).
In Figure 2, the top three curves reflect changes in pressure during the cardiac cycle in the aorta, atria and ventricles respectively. The fourth curve demonstrates changes in the volume of blood flow in the ventricles. The fifth curve depicts the changes in the electrocardiogram (ECG) over the cardiac cycle.

**Atria as primer pumps**

The atria continuously receive blood from the great veins i.e. the superior and inferior vena cavae and the pulmonary veins. Approximately 75 percent of this blood flows directly into the ventricles without atrial contraction. The atria act as primer pumps by pumping the additional 25 percent of the blood and thereby increasing the efficiency of the ventricular contraction.
Pressure changes in the atria

From figure 2, it can be noted that there are three distinguishable pressure changes in the atria during the cardiac cycle. The ‘a wave’ occurs during atrial contraction. The right atrial pressure increases by 4 to 6 mm Hg while the left atrial pressure increases by about 7 or 8 mm Hg causing an overall increase in atrial pressure. The ‘c wave’ occurs during ventricular contraction when a slight backflow of blood occurs from the ventricles into the atria. This occurs due to the backward bulging of the A-V valves due to ventricular systole. The ‘v wave’ occurs toward the end of the ventricular systole. At this point, there is a slow flow of blood into the atria while the A-V valves are closed thus causing a pressure elevation. Upon completion of ventricular systole, the A-V valves open causing blood to flow into the ventricles and the v wave disappears.

Ventricles as pumps

Filling of ventricles during diastole

At the end of the contraction, during diastole, the heart relaxes and pressure in the ventricles falls. AV valves are pushed open by the moderate pressure gradient between the atria and ventricles and blood rapidly flows into the ventricles. There is an increase in ventricular volume as shown in figure 2. This period is referred to as the period of rapid filling of the ventricles and lasts for the first third of diastole.
During the middle third of diastole, a small amount of blood flows into the ventricles. This is the blood that is continuously received by the atria from the superior and inferior vena cavae and pulmonary veins which then flows into the ventricles.

During the last third of diastole, the atria contract and cause the remaining ~25% of the blood to flow into the ventricles.

**Emptying of ventricles during systole**

Systole can be divided into the period of isovolumic contraction, period of ejection and period of isovolumic relaxation.

**Period of isovolumic/ isometric contraction**

When contraction begins, the pressure inside the ventricles increases sharply and causes the AV valves to close. For an additional 0.02 to 0.03 second, the ventricular pressure continues to increase until it is sufficient to push open the aortic and pulmonary valves. During this time, the pressure inside the ventricle increases but volume of blood remains constant. Hence, this is referred to as the period of isovolumic/ isometric contraction.

**Period of ejection**

When the left ventricular pressure is about 80 mm Hg and the right ventricular pressure is about 8 mm Hg, the semilunar valves are pushed open and blood flows
into the arteries. Approximately 70 percent of the blood is emptied during the first third of this period and is called the period of rapid ejection. The remaining 30 percent is emptied in the last two thirds and is called the period of slow ejection.

*Period of isovolumic relaxation*

At the end of the ventricular contraction, diastole begins and ventricular pressures drop sharply. The higher pressures in the aorta and pulmonary arteries close the semilunar valves. Ventricles continue to relax for the next 0.03 to 0.06 second. During this period, the ventricular pressure decreases while the ventricular volume remains constant. When the pressures reach diastolic levels, the A-V valves open and the next cycle begins.

*Aortic pressure curve*

When the left ventricle contracts, ventricular pressure increases rapidly and opens the aortic valve. Blood is ejected into the aorta following which the ventricular pressure increases less rapidly. Blood flow through the aorta stretches the arterial walls and pressure rises to about 120 mm Hg. At the end of ventricular contraction, the aortic valve closes but the arteries maintain a high pressure even during diastole. As seen in figure 2, a cleft is seen in the pressure curve when the aortic valve closes. This is because of the short period of backflow of the blood from the aorta into the left ventricle before the closure of the valve followed by the sudden cessation of blood flow. When the valve closes, the aortic pressure slowly decreases as the blood enters systemic circulation. The pressure falls to
about 80 mm Hg before the next cycle of ventricular contraction. A similar pressure curve is seen in the pulmonary artery, except the pulmonary pressures are one-sixth the aortic pressures.

**Electrocardiogram (ECG)**

As discussed earlier, the cardiac cycle begins with the generation of an action potential in the sinus node which travels through the atria, AV node and then through the ventricles. This electrical activity is depicted in the electrocardiogram (ECG). The ECG comprises the P wave, the QRS complex and the T wave (Figure 2). The P wave corresponds to the depolarization of the atria during which there is an increase in atrial pressure. The onset of the QRS complex, corresponding to the depolarization of ventricles, is seen after about 0.16 seconds and is followed by ventricular contraction. Thus, the QRS complex begins slightly before ventricular contraction. The T wave corresponds to the event of repolarization of the ventricles which results in ventricular diastole. Therefore, the T wave precedes ventricular diastole. Diastole completes the cycle and represents the phase of relaxation and passive filling of the atria and the ventricles. Electrical activation drives mechanical contraction and hence ECG based indices precede their mechanical counterparts (Guyton and Hall 2003).
2.1.5. Pressures in the circulatory system

Blood pressure

Blood pressure is defined as the force exerted by blood against the wall of the blood vessel. It is measured in millimeters of mercury (mm Hg) as the mercury manometer has been the standard reference for blood pressure measurement. If the pressure difference between two points in a blood vessel is 1 mm Hg and blood flow is 1 ml/sec, then resistance to blood flow is 1 Peripheral Resistance Unit or 1 PRU.

![Diagram of blood pressure in different portions of the circulatory system](image)

*Figure 3: Normal blood pressure in different portions of the circulatory system (Guyton and Hall 2003)*

In the systemic circulation, the left ventricle pumps blood into the aorta and as a result, aortic pressure is very high. Since the heart pumps blood in a pulsatile manner, the aortic pressure varies between 120 mm Hg during systole and 80 mm
Hg during diastole with a mean pressure of about 100 mm Hg. As blood flows from the arteries into the arterioles, capillaries and veins, blood pressure gradually decreases and is close to 0 mm Hg in the veins (as shown in Figure 3). Average functional capillary pressures are about 17 mm Hg. In an adult male, blood flow is 100 ml/sec and the pressure difference between systemic arteries and veins is 100 mm Hg. Therefore, resistance to blood flow in systemic circulation is 1 PRU. In certain conditions, blood vessels can strongly constrict and exhibit resistances as high as 4 PRU or they can dilate and exhibit resistances as low as 0.2 PRU.

Pulmonary circulation also exhibits a similar pressure curve except the pressures here are much lower. As blood flows from the right ventricle into the pulmonary artery, pulmonary arterial pressures ranges between 25 mm Hg systolic pressure and 6 mm Hg diastolic pressure with a mean arterial pressure of 16 mm Hg. The mean pulmonary capillary pressure averages around 7 mm Hg. The pressure difference between the pulmonary artery and the right atrium is about 14 mm Hg while blood flows at about 100 ml/sec. Therefore, resistance to blood flow in pulmonary circulation or total pulmonary vascular resistance is 0.14 PRU. An increase in blood pressure can be expected to increase the rate of blood flow by increasing the force that causes the flow, distending the blood vessels and decreasing vascular resistance.
Although the same amount of blood enters pulmonary and systemic circulations, pressures in pulmonary circulation are much lower as blood has to travel only a short distance between the heart and the lungs.

**Vascular distensibility**

Vascular distensibility is an important property exhibited by blood vessels and is the ability of the arteries to be distended or stretched under pressure. It is expressed as the fractional increase in blood volume for an increase in blood pressure of 1 mm Hg. An increase in blood flow occurs not only as a result of increased blood pressure but also decreased vascular resistance caused by vascular dilation. Vascular distensibility also accommodates the pulsatile output of the heart and averages out the pulsations to ensure a continuous and smooth flow of blood in the arteries.

**Difference in arterial and venous distensibilities**

Arteries have thicker walls when compared to veins. As a result, veins are about eight times more distensible than arteries and can hold eight times more blood than arteries of comparable size. Pulmonary arteries operate under pressures one-sixth of the systemic arteries. Therefore, they possess greater distensibilities i.e. six times greater than systemic arteries (Guyton and Hall 2003).
Vascular compliance

Vascular compliance is the total volume of blood that can be stored in a blood vessel for each mm Hg increase in pressure. Compliance is expressed as distensibility times volume. A systemic vein is about 8 times as distensible as a corresponding artery with a volume of about 3 times. Its compliance is therefore 24 times that of the artery (Guyton and Hall 2003).

2.1.6. Arterial pressure pulsations

With each heartbeat, blood flows into the arteries. Arterial distensibility ensures that blood flows to the tissues throughout the cardiac cycle as opposed to only during the cardiac systole. Arterial compliance ensures reduction in pressure pulsations by the time blood reaches the capillaries. Therefore, blood flow to the tissues is continuous.

Figure 4: Pressure pulse contour recorded at the root of the aorta (Guyton and Hall 2003)
Figure 4 depicts pressure pulsations at the root of the aorta. In a healthy adult, the peak of each pulse (systolic pressure) is 120 mm Hg and the lowest point of the pulse (diastolic pressure) is 80 mm Hg. The difference between systolic and diastolic pressure is pulse pressure and is normally around 40 mm Hg.

Pulse pressure is affected by:

a. Stroke volume output of the heart

Stroke volume output of the heart is the volume of blood that the ventricles empty into the arteries during systole and is usually about 70 ml. An increased stroke volume output of the heart increases the volume of blood to be accommodated in the arteries with each heartbeat causing a greater rise and fall of pressure during the cardiac cycle, resulting in greater pulse pressure.

b. Arterial compliance

Lesser arterial compliance indicates a higher pressure for a given stroke volume of blood. Pulse pressure is almost double in old age as arteries may have become hardened by arteriosclerosis and will exhibit less compliance.

Pulse pressure can therefore be estimated by the ratio of the cardiac stroke volume output and arterial compliance. Conditions that affect these two factors in the circulatory system will also affect pulse pressure.
Abnormal pressure pulse contours

Some pathological conditions in the circulatory system such as aortic stenosis, patent ductus arteriosus and aortic regurgitation cause abnormal contours in the pressure pulse wave.

In aortic stenosis, the size of the opening of the aortic valve is reduced due to acute rheumatic fever or calcification of the aortic valve. The pressure pulse is significantly reduced because of decrease in flow of blood. Patent ductus
arteriosus is a congenital disorder where more than half of the blood pumped into the aorta by the left ventricle flows backward through a ductus into the pulmonary artery and then to the lungs. Due to this, there is a severe drop in diastolic pressure. In aortic regurgitation, there is incomplete closure of the aortic valve and when the left ventricle pumps blood into the aorta, blood immediately flows back into the ventricle. Aortic pressure could fall as low as 0 mm Hg. A cleft is not seen in the pressure pulse contour as the aortic valve does not close or is absent.

**Transmission of pressure pulses to peripheral arteries**

When the left ventricle pumps blood into the aorta during systole, only the proximal portion of the aorta is distended due to inertial action of blood. This prevents it from flowing to the periphery at once. Increasing pressure in the aorta gradually causes this distention to spread resulting in the transmission of the pressure pulse to peripheral arteries.

The velocity of transmission of pressure pulse is 3 to 5 m/sec in the aorta, 7 to 10 m/sec in larger arteries and 15 to 35 m/sec in small arteries. Pulse wave velocity is inversely proportional to arterial compliance. This is why the aorta has the lowest velocity of pressure pulse transmission. Also, pulse wave velocity in the aorta is about 15 times greater than the velocity of blood flow as the pressure pulse is a wave of pressure and involves little or no movement of blood.
Damping of pressure pulses in smaller arteries

As the pressure pulse moves from larger arteries to arterioles and capillaries in peripheral organs, the intensity of pulsations gradually reduces. In cases of large aortic pulsations or greatly dilated arterioles, pulsations may be detected in capillaries. The gradual reduction in pulsations from the aorta to the periphery is referred to as ‘damping of pressure pulses’.

Two factors result in damping:

- Vascular resistance to blood flow
  
  For pulsations to occur, a small amount of blood should flow ahead of the pulse wave front to distend the next portion of the blood vessel. A greater vascular resistance, the more difficult it is for blood flow to distend the artery.

- Vascular compliance
  
  Vascular compliance damps pulsations because an increase in compliance implies that a greater amount of blood is required at the pulse wave front to cause pulsations.

Since these factors vary directly with pulsations, it can be concluded that damping is directly proportional to the product of vascular resistance and compliance (Guyton and Hall 2003).
2.2. Technology platform

2.2.1. Theory of pulse transit time

Pulse transit time (PTT) is the time taken for the pressure pulse to travel from the aortic valve to the periphery. More specifically, PTT is the time delay between the R-wave of the ECG and the onset of the pulsation at a selected peripheral site detected by a sensor.

![Diagram showing the measurement of PTT using the R wave of the ECG](Smith, et al. 1999)

**Figure 7: Diagram showing the measurement of PTT using the R wave of the ECG (Smith, et al. 1999)**

**Principle**

Consider a rigid tube of length ‘d’ with negligible pressure losses connected to a cyclic pump.
Let the liquid pumped flow through the tube at velocity ‘v’. Time ‘t’, taken for the pressure pulse to travel from the pump to the end of the tube can be calculated by

\[ t = \frac{d}{v} \]

This concept can be extended to the human body to determine PTT and estimate blood pressure as the heart pumps blood to the tissues in the body through tubular structures or arteries. The added complexities in the human system would include variations in elasticity of blood vessels (due to vascular distensibility), vessel dimensions and various pathological conditions that may alter heart and vascular mechanical properties.

According to the Moens–Korteweg’s formula, pulse wave velocity, vessel dimensions and vascular distensibility are related by:

\[ v = \sqrt{\frac{Ea}{\rho d}} \]  \hspace{1cm} (1)

\( v \) is the pulse wave velocity,

\( E \) is the elastic modulus of the vessel,

\( \rho \) is the density of blood,

\( a \) is the wall thickness, and

\( d \) is the interior vessel diameter.
Elastic modulus $E$ exponentially increases with blood pressure $P$ as:

$$E = E_0 e^{\gamma P}$$  \hspace{1cm} (2)

$E_0$ is the elastic modulus at zero pressure,

$\gamma$ is a coefficient ranging from 0.016 to 0.018,

Combining Eqs. 1 and 2 and substituting velocity with $v = K/T$, where $K$ refers to the distance for the pulse wave to transit within time $T$:

$$P = \frac{1}{\gamma} \left( \ln \frac{dK^2}{aE_0} - 2\ln T \right)$$  \hspace{1cm} (3)

Considering changes in $a$, $d$, and $E_0$ to be negligible, an inverse relationship can be drawn between blood pressure and pulse wave transit time (Ahlstrom, et al. 2005)

$P \propto 1/T$

The inverse relation can be explained as follows:

An increase in blood pressure lowers arterial compliance which in turn results in faster transmission of the pulse. On the other hand, a decrease in blood pressure increases vascular compliance and slows down pulse transmission. However, more research is necessary to relate absolute values of PTT with absolute values of blood pressure. At present, PTT can be used to predict changes or fluctuations in blood pressure (Smith, et al. 1999).
PTT includes the time delay between the R wave of the ECG and the opening of the aortic valve i.e. the period of ventricular isometric contraction or the pre-ejection period (PEP). PEP is dependent on blood pressure, ventricular stroke volume and co-existing cardiac diseases. Some dispute surrounds the correlation between PEP and blood pressure as certain results indicate that PEP should be excluded from PTT calculations while certain others indicate that PEP is significant to the co-relation between PTT and blood pressure.

**2.2.2. Pathological conditions that affect blood pressure**

Continuous blood pressure monitoring is important in hospitalized patients as changes in pressure indicate several pathological conditions that require immediate medical attention. The high rates of incidence and hospitalizations associated with these diseases emphasize the importance of better and improved monitoring facilities.

**Hypertension**

Hypertension is characterized by an elevated blood pressure. About 75 million people in the United States were diagnosed with hypertension in 2006 and approximately 60,000 people died as a consequence of it (American Heart Association 2006).

Changes in pressure flow hemodynamics are seen in the early phases of hypertension due to altered properties of blood vessels such as constriction.
Pressure differences are seen as a result of changes in arterioles that cause an increase in total peripheral resistance and changes in arteries that cause a decrease in arterial compliance (OS 1991).

**Myocardial infarction**

Myocardial infarction or heart attack is a medical condition with an interruption in blood supply to the heart causing death of heart cells. It is mostly caused by arterial occlusion by plaque - a collection of lipids and white blood cells. The frequency of myocardial infarction is approximately 1.5 million each year with an associated mortality rate of 30% (eMedicine 2010).

Blood pressure is continuously monitored in patients who have suffered myocardial infarction. Changes in blood pressure are accompanied by other symptoms such as chest pain, tachycardia, arrhythmias and shortness of breath. Effects of myocardial infarction include systolic/diastolic dysfunction, a decreased cardiac output, increased systemic vascular resistance, increase in blood volume, etc. Loss of myocardium impairs the activity of the heart that reduces cardiac output. In severe cases, it may result in cardiac shock. Intense pain and anxiety activate the sympathetic nervous system which causes constriction of blood vessels and cardiac stimulation leading to hypertension and tachycardia. Tachycardia results in rapid heart rates causing a sharp drop in cardiac output and blood pressure. This may further lead to coronary ischemia (restriction in blood supply) and extension of the infarct (Klabunde 2007).
**Pneumonia**

Pneumonia is a medical condition where an abnormal inflammation of the lung is seen. Infectious pneumonias are caused by invasion of the lung by microorganisms. In 2004, there were 1.3 million hospitalizations associated with pneumonia in the United States (Centers for Disease Control and Prevention 2006).

Blood pressure is one of the parameters constantly monitored in patients with pneumonia. Symptoms include low blood pressure, low body temperature, increased respiratory rate, a high heart rate and low oxygen saturation. Some patients have severe difficulty in breathing, or have cyanosis (blue-tinged skin) and require immediate medical attention (Metlay, Kapoor and Fine 1997).

**Obstetrical procedures**

Spinal anesthesia is used to relieve pain in obstetrics. It is known to cause rapid and substantial changes in blood pressure. High and low blood pressures are seen during delivery and there is a need to constantly monitor pressure. (Foo and Wilson 2009). In 2004, there were ~7 million obstetrical procedures performed with 1.3 million cesarean sections (Centers for Disease Control and Prevention 2006).
Respiratory dependent blood pressure changes

PTT can be used to measure changes in respiratory effort caused by augmented upper airway resistance in children. It can be used to monitor tidal breathing BP changes, assess breath based BP changes and detect abnormal pressures. During tidal or normal breathing, the changes in intra-thoracic pressure and lung volume have an effect on cardiac pre-load and after load. Also, changes in ventilation (rate at which gases enter and leave the lungs) and pleural pressures affect venous return and cardiac output. Together, these may lead to blood pressure fluctuations.

Respiratory dependent blood pressure variations can result from status asthmaticus, pericardial effusion, and hypovolemia.

*Status asthmaticus:* Status asthmaticus is an acute form of asthma where an increase in lung volume occurs as a result of an increase in airflow resistance. This, accompanied by decreased pressure of oxygen and increased volume of carbon dioxide in blood, can lead to cardiac arrest. In 2008, 16.4 million adults and 7 million children were diagnosed with asthma (Centers for Disease Control and Prevention 2009).

*Pericardial effusion:* Pericardial effusion is a condition where an abnormal accumulation of body fluid surrounds the heart, increasing the pressure on the heart. This leads to a series of events such as a decrease in diastolic filling of ventricles, increase in arterial stiffness and heart rate (Foo and Wilson 2009).
Shock

Shock is life threatening condition that occurs due to a severe drop in blood pressure, too low to sustain life. There are three types of shocks:

Hypovolemic Shock: Hypovolemia is a medical state of decreased blood volume in the body. A lower than normal volume of blood enters the atria during the cardiac cycle, resulting in low volume of blood pumped by the heart. Blood volume may be drastically reduced due to external bleeding (accidents), internal bleeding (stomach ulcer or a ruptured ectopic pregnancy) and an excessive loss of body fluids (due to major burns, pancreatic inflammation, and intestinal perforation). It is identified by an elevated pulse, low blood pressure, lack of perfusion or nutritive delivery to the capillaries, anxiety, confusion and rapid breathing.

Cardiogenic Shock: In the state of cardiogenic shock, there is inadequate pumping activity of the heart resulting in low volumes of blood being pumped with each heartbeat. Inadequate cardiac activity can be a result of heart attack, pulmonary embolism (blood clot in the lungs), malfunction of a heart valve, rupture of the septum, cardiac arrhythmias or cardiac tamponade (compression of the heart due to pericardial effusion). Cardiogenic shock is seen in about 5-10% patients with acute myocardial infarction (Sharma 2008).

Distributive Shock: Septic shock is the most common form of distributive shock and is the leading cause of non-cardiac deaths in ICUs. Distributive shock can
also occur as a consequence of toxic shock syndrome (TSS), anaphylaxis, drug or toxin reactions (e.g. insect bites), etc. Sepsis is seen in more than 750,000 patients annually.

Inadequate nutritive delivery is seen in distributive shock due to decreased systemic vascular resistance and a high cardiac output. Peripheral vessels demonstrate changes in their contraction and dilation. Early septic shock is characterized by reduced diastolic blood, widened pulse pressure, flushed warm extremities and an increased cardiac output. Late septic shock is characterized by the combination of myocardial contraction and peripheral vascular paralysis causing a hypoperfusion of critical organs (Kanaparth and Lessnau 2009).

**Stroke**

Stroke is a medical condition that occurs when blood supply stops to a region in the brain, giving rise to a loss in neurological function. The brain requires 15-20 % of the total resting cardiac output to function normally. Conditions like thrombosis (occlusion of blood vessel by a blood clot), embolism (migration of arterial block) and hypoperfusion can limit the blood supply to the brain. A decrease in blood flow ceases neuronal function. Patients who have suffered stroke are hypertensive at the baseline and may show a further increase in blood pressure. Cardiac arrhythmias, congestive heart failure and other acute cardiac conditions are seen in stroke patients (Manaker 2007).
Approximately 800,000 people have a stroke annually in the United States (Lloyd-Jones, Adams and Carnethon 2009). In 2006, it caused 137,000 people to die. It is the third leading cause of death in the nation (Centers for Disease Control and Prevention 2009).

**Congestive heart failure**

In Congestive Heart Failure (CHF), the heart is unable to pump blood at the rate required by the metabolizing tissues or can do so only at an elevated pressure. This occurs due to a defect in cardiac filling or emptying. Cardiac activity is compensated by certain mechanisms such as:

- Increase in ventricular end-diastolic volume and pressure
- Increase in volume and pressure in the atrium behind the failing ventricle.
- Vigorous contraction of the atrium
- Increase in pressure in the venous and capillary beds behind (upstream to) the failing ventricle
- Increase in fluid transfer from the capillary bed into the interstitial space

Although the situation is temporarily controlled, cardiac capability progressively deteriorates (Singh 2008). In 2006, there were 5.7 million people diagnosed with CHF with 300,000 deaths in 2005 (American Heart Association 2009).

**Renal failure**

Renal failure is a medical condition where the kidneys fail to function. Glomerular pressure depends on renal blood flow (RBF) and is controlled by
afferent and efferent arteriole resistance. A reduced Glomerular Filtration Rate is maintained by renal efferent vasoconstriction. Decreased renal perfusion can be easily identified by hypotension and tachycardia. Prerenal failure can be caused by a decrease in effective arterial blood volume (Hypovolemia, CHF, liver failure, sepsis) and renal arterial disease (Peacock 2009).

An estimated 23 million adults were diagnosed with chronic kidney disease between 1999 and 2004. In 2006, there were 90,000 deaths associated with end stage renal disease (National Institute of Diabetes and Digestive and Kidney Diseases 2009).

2.3. Product description

Figure 8: EverOn™

EarlySense’s patient supervision system ‘EverOn’ consists of a replaceable sensor and a bedside monitor as shown in Figure 8. The contact-free sensor is placed below
the patient’s mattress and the bedside unit displays ongoing clinical data and trends, and alerts care providers when vital signs - heart rate and pattern, respiratory rate and pattern and body movement, exceed predefined thresholds. This is illustrated in Figure 9.

![Image of a monitor displaying heart rate and respiration rate](image)

**Figure 9: Parameters detected by EverOn**

Chronic diseases such as asthma, chronic obstructive pulmonary disease (COPD), sleep apnea, cystic fibrosis (CF), epilepsy and heart failure affect breathing and cardiac activity. These diseases interfere with the normal respiratory and cardiac functioning and result in abnormal breathing and heart rate patterns which are recognized by EverOn (Halperin, et al. 2008).

Body movement/motion is the third parameter that is monitored by the system. A low rate of body movement is associated with pressure ulcer risk. Pressure ulcers are lesions caused by continuous pressure exerted on a body part resulting in damaged tissue. A high rate of body motion indicates agitation or pain experienced by the
EverOn identifies whether a patient is in or out of bed and alerts nurses about patient movement thus preventing pressure ulcers and patient falls.

EarlySense now wishes to introduce non-invasive, continuous blood pressure monitoring into the device function. Blood pressure is a constantly monitored parameter in hospitalized patients. It is recorded on a four hourly basis on an average in general medical and surgical ward patients. By incorporating this additional application, EverOn will reduce the burden on overworked nurses and help hospital-based physicians improve their clinical decision-making ability, using accurate data instead of relying on infrequent measurements of vital signs recorded by nurses.

**Components of the system** (Halperin, et al. 2008)
As depicted in Figure 10, the system comprises a motion sensor 30, a control unit 14 and a user interface 24. The motion sensor is not in direct contact with the patient’s body and can comprise a ceramic piezoelectric sensor, a strain sensor, a vibration sensor or a pressure sensor. For certain applications, the sensor may comprise a standard communication interface such as a USB port to enable connection to standard monitoring equipment. The user interface is either integrated into the control unit or is in a remote location.

Control unit

The control unit comprises the data acquisition module 20 and the pattern analysis module 16. The data acquisition module non-invasively monitors the breathing and

Figure 11: Components of the control unit (Halperin, et al. 2008)

The control unit comprises the data acquisition module 20 and the pattern analysis module 16. The data acquisition module non-invasively monitors the breathing and
heartbeat patterns of the subject. The pattern analysis module comprises one or a combination of the following modules: breathing pattern analysis module 22, heartbeat pattern analysis module 23, cough analysis module 26, restlessness analysis module 28, and blood pressure analysis module 29. The breathing pattern analysis module will extract breathing patterns from the motion data, the heartbeat pattern analysis module will extract heartbeat patterns and so on. The patterns are analyzed to:

- Predict the occurrence of an event such as asthma, sepsis, cardiac arrest, respiratory depression
- Monitor the intensity and progression of the event

**User interface**

The user interface comprises a display unit such as an LCD or CRT monitor. It can comprise a wireless or wired communication port such as a telephone line, internet or another wide area network to transfer the acquired data to a remote site where the information can be analyzed and interpreted. Upon the occurrence of patient complications, the user interface alerts a healthcare worker. Prediction of such approaching events will ensure timely physician intervention and lower morbidity and mortality of patients. For instance, timely prediction of patient deterioration in the general ward could prevent the need to transfer him/her to the intensive care units thereby shortening hospital stay and lowering morbidity.
**Working**

Changes in blood pressure are detected by using two motion sensors. With reference to Figure 10, the first motion sensor is placed either below the abdomen (38) or below the chest (39) and the second motion sensor is placed in the vicinity of the legs (40).

The pulse detected by the sensor below the chest is the ‘valve point’. At this point, the aortic valve opens and blood flows into the aorta. Sometimes, two close peaks indicating the opening of the aortic and the pulmonary valves may be seen. The pulse travels through the mattress at the speed of sound which means that the sensor detects the pulse almost immediately with a delay of less than 6 msec. The peak detected by the second sensor is called the ‘pressure point’. This occurs when the pulse reaches the extremity, say the leg, and is once again detected almost immediately by the sensor. The time taken for the pulse wave to progress from the heart to the extremity i.e. from valve point to pressure point is used to calculate PTT and in turn blood pressure. The distance between the two sensors is necessary for this calculation. Either this distance is fixed and the physician installing the system places the sensor at the mentioned distance, or the physician inputs the distance into the device after placing the sensor.

Measurement of PTT (Proprietary data)

![Figure 12: Measurement of PTT using motion sensors (Halperin, et al. 2008)](Proprietary data)
PTT and blood pressure

The above figures illustrate the Mean Arterial Blood Pressure (MAP) reference signal (A), the corresponding PTT between an ECG device and a pulse oximeter\(^1\) (B) and the corresponding PTT between a contact-free motion sensor and a pulse oximeter (C). From the graphs, it can be observed that when MAP increases between 450 and 650 seconds, a corresponding decrease is seen in PTT in Figures 13B and 13C. Likewise, a decrease in MAP between 650 and 850 seconds results in a corresponding increase in PTT, again seen in both figures. The system identifies these changes in blood pressure and alerts caregivers (Halperin 2008).

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\(^1\) Pulse oximeter is a medical device that measures the oxygen saturation in a subject’s blood.
3. Description of the commercialization plan

The commercialization plan describes the need for the technology, industry trends, target market of the device and strategic steps towards launch of the product.

3.1. Need for smart patient supervision systems

Inefficient patient monitoring in hospitals results in preventable patient complications such as pressure ulcers and patient falls. A shortage in nursing staff has contributed to poor patient care. In 2008, there were 116,000 registered nurse vacancies. The shortage is projected to increase to 1 million nurses by 2020. (American Hospital Association 2008). A majority of non-ICU patient beds are unmonitored due to this shortage. Preventable patient complications are not reimbursed by payors and increase hospital costs. As of October 1, 2008, Medicare stopped reimbursement to hospitals for preventable patient complications (Gever 2008).

Regulatory and accreditation agencies have laid increased emphasis on patient care and safety. The Joint Commission Guideline 16 states that hospitals should “Improve recognition and response to changes in a patient’s condition”. (The Joint Commission 2008). There is a need for hospitals to adopt practices that help reduce in-hospital morbidity and other preventable complications.

Studies have indicated that patient deterioration can be reduced by improved monitoring and care facilities in hospitals (Needleman, et al. 2002). Vital signs are
monitored in general ward patients every four hours (Zeitz and McCutcheon 2006). With the shortage of nursing staff, patient deteriorations will remain undetected leading to complications and adverse events. As higher acuity patients are more quickly moved to lower acuity wards, the need for smart patient supervision becomes more important.

3.1.1. Need for blood pressure monitoring

Changes in blood pressure are considered an indication of patient deterioration. It is one of the parameters measured as part of the ‘Early Warning Scoring System’ (EWSS) tool for physician intervention in cases of patient deterioration. Blood pressure, heart rate and respiratory rate are included in the EWSS (Sharpley and Holden 2004). Fluctuations in blood pressure can occur as a result of pathological conditions such as myocardial infarction, stroke, renal complications and trauma. Cardiac arrest is most commonly preceded by arterial hypertension or hypotension. Early identification of these blood pressure fluctuations will prevent complications in patient health. Alerting caregivers immediately enables early interventions by physicians, which will lead to reduced complications and costs.

3.2. Value proposition

EverOn is a contact-free, patient supervision system that saves hospital costs. Preventable patient complications such as pressure ulcers and patient falls are no longer reimbursed by Medicare. EverOn will continuously monitor a patient’s vital...
parameters, alert nurses upon patient deterioration and save costs for the hospitals by preventing the occurrence of adverse events.

Moreover, EverOn addresses the issue of staff shortage. It eliminates the presence of a care provider by a patient at all times and helps nurses in prioritization of patients and effective utilization of time. Physicians will benefit as they will have access to continuous information about the patient’s condition helping them make more informed decisions. The patient experiences non-imposing supervision, peace of mind and a short stay at the hospital. The payer or administrator benefits from a reduced length of the patient’s stay in the hospital, low cost supervision and low liability for preventable complications.
3.3. Patient monitoring market

3.3.1. Overview

Figure 14: Segment analysis of the patient monitoring industry (Frost and Sullivan 2008)

The patient monitoring market generated $7.03 billion in 2007 and is expected to grow at a compound annual growth rate (CAGR) of 7.2% till 2012 in North America. This market encompasses all equipment that is capable of measuring vital parameters continuously or intermittently, from low-tech equipment to highly sophisticated, multi-parameter devices. Devices include multi-parameter monitoring equipment, cardiovascular monitoring equipment, sleep apnea monitoring equipment, blood pressure monitoring equipment, hospital wireless patient monitoring equipment, etc. Figure 14 analyzes revenues generated by the
various segments of the patient monitoring market. Sleep apnea monitoring equipment demonstrates the highest growth in this industry, the reason being that this is a largely undiagnosed market with high prevalence of the disease and thus presents high growth opportunities. (Frost and Sullivan 2008)

3.3.2. Revenue forecasts for patient monitoring industry

![Chart 2.2](image)

**Figure 15: Revenue projections for the North American patient monitoring equipment market (Frost and Sullivan 2008)**

The multi-parameter patient monitoring industry shows a CAGR of 2.6 percent from 2007 to 2012 in North America. 2007 revenues were about $975 million and are expected to reach approximately $1.15 billion in 2014. Revenues are the product of number of units shipped and the average price per unit. The market trends for this segment indicate that it is a mature market with high saturation. A
steady and slow growth is seen due to an increase in demand for these products accompanied by a reduction in their prices. A well established customer base and defined monitoring budgets will favor steady growth. Currently, the focus of the patient monitoring industry is shifting from higher acuity units to lower acuity areas.

Unit and demand analysis

In 2007, around 85,000 units of patient monitoring equipment were shipped and an increase of 3.3 percent over the previous year was seen. Around 110,000 units are expected to be shipped in 2014 with the market showing a CAGR of 3.5 percent from 2007 to 2014. A steady growth is expected in unit demand, with
declining prices and increasing focus on lower acuity wards acting as favorable factors. Lower unit prices will drive sales and focus on lower acuity wards will result in the installation of these monitors in these wards. (Frost and Sullivan 2008)

3.3.3. Favorable trends

Hospitals’ need for sophisticated patient monitoring devices

Figure 17: Supply and demand of nurses (Frost and Sullivan 2008)

Hospital trends in the United States show increasing acuity levels in patients, thereby resulting in over-populated emergency and critical care units. Figure 17 illustrates the gap between nurse supply and demand. By 2020, the demand of nurses will exceed supply by 1 million. This is where automated patient monitoring equipment comes into play. It will help nurses leverage their time by
eliminating documentation tasks and focusing on patient care alone. Incorporating information technology into these systems will directly save patient information in their records. An increase in patient population in higher acuity environment can be reduced by wireless patient monitoring. With these systems in place, patients can be monitored at any hospital location.

**Increasing emphasis on patient safety by regulatory agencies**

Regulatory agencies have placed increased emphasis on patient safety. The Joint Commission Guideline 16 states that hospitals should improve their recognition and response to changes in health status of patients. The occurrence of adverse clinical events is preceded by warning signs 6 to 8 hours prior to the incident. It is estimated that 4-17% of patient admissions show critical events. Detecting early patient deterioration signs for ICU transfer can reduce mortality by 75% and cost of care by 40%. (Kaboli and Rosenthal 2003)

**Convergence of Information Technology (IT) and patient monitoring systems**

With increasing emphasis on electronic medical records, patient monitoring companies are trying to integrate IT into their devices. They can do so by either directly integrating IT into existing devices or using software modules that can be interfaced to the systems.
Improving cost containment for hospitals

Non-invasive blood pressure monitoring addresses cost containment issues of hospitals. With multi-parameter patient monitoring systems coming into the picture, hospitals can save several preventable patient complications. If a hospital can avoid a patient complication such as a fall/ injury caused by the patient getting up from bed, the treatment cost incurred by the hospital by this fall will not be reimbursed by the Centers for Medicare and Medicaid Services. In 2008, Medicare stopped paying hospitals for preventable complications. There is a large immediate market opportunity for this product.

3.3.4. Market restraints

Decreasing Hospital Beds Limit Market Potential

A decreasing trend in hospital beds is seen in the United States and this could limit the number of multi-parameter device sales. A hospital can support only ‘X’ number of beds which acts as an upper limit for the number of monitors purchased by hospitals.

Group purchasing organizations overpower smaller manufacturers

All major companies that produce automated monitoring devices such as GE, Welch Allyn, Datascope, and Philips, use group purchasing organizations (GPOs) as their distribution channels. This gives them an advantage over small manufacturers who find it very difficult to penetrate and reach out to the
customers/ hospitals. GPOs, such as Premier, Consorta, and Broad Lane, can prevent competition for large companies by means of their purchasing contracts with hospitals.

Possible incompatibility between patient monitors and Hospital Information Systems (HIS)

HIS in the United States is very varied and comprises wired and wireless infrastructure or may rely on paper alone. Multi-parameter patient monitoring device companies should ensure that their devices can be adopted in any kind of HIS but this may result in several hurdles such as liability. Since patient safety is of prime importance, companies are not sure if they can achieve compatibility with a hospital’s open information system as it is not under their control. This incompatibility between HIS and patient monitors will pose a significant delay in adoption. (Frost and Sullivan 2008)

Limited medical reimbursement

Lack of or poor reimbursement is one of the most important market restraints for growth. Although these multi-parameter monitoring devices and automated blood pressure monitoring devices serve several clinical purposes, adoption of these devices by hospitals is limited. While the recent Medicare and Medicaid reimbursement for ambulatory blood pressure monitors for white coat hypertension has encouraged growth of these devices, the amount is not sufficiently attractive.
Hospitals are weighed down by their financial situations

Hospitals have been hit hard by the economic downturn. They have issued strict spending cutbacks and have resorted to consolidation between hospitals. Device manufacturers are now posed with the challenge of reduced potential selling sites and are finding ways to aggressively sell their products despite these constraints.

3.4. Competition analysis

Patient supervision systems similar to EverOn are being manufactured. Although these systems measure heart rate, respiratory rate and body movements, only EverOn will have the added functionality of blood pressure monitoring. A summary of these systems and EverOn’s competitive advantage is provided below.

Competitors:

Hoana Medical, Inc.: LifeBed™ Patient Vigilance System

Hoana Medical, Inc. is a privately held medical device company headquartered in Honolulu, Hawaii. Their product, LifeBed Patient Vigilance System is a contact-free patient supervision system that monitors a patient’s vital signs – heart rate and respiratory rate. When the patient’s vital parameters fall below the threshold, the system alerts nurses using the hospital call system. It tracks patient heart rate from 35 to 200 beats per minute and respiratory rate from 4 to 70 breaths per minute with customizable upper and lower alert limits. It also detects bed exits. The device is for use in primary acute care hospitals in medical and surgical wards. It uses 16 piezoelectric sensors and strain gauges and is FDA & CE cleared. The company
intends to rent the monitoring system at $6000-$7000 per year (Hoana Medical Inc.).
The company has eight patents issued for its monitoring system (USPTO 2010).

Although Hoana Medical is EarlySense’s most established competitor, their sensor is very complex and expensive when compared to EverOn.

**Emfit Ltd: Discreet Vitals Monitoring**

Emfit Ltd is a Finland based company. It is a manufacturer of ferroelectret sensors and related embedded sensor systems. The company has separate monitors for epilepsy, vital signs, falls and wandering, and movement. Their product, Discreet Vitals Monitoring, can detect heart rate, respiratory rate and bed exits and uses a Piezo-film sensor. It is a Class I device which means that it presents minimum potential harm to the user and has made sales in Europe. (Emfit Ltd.). The company has one design patent and four utility patents issued for the their device (USPTO 2010).

**BiancaMed: Baby monitor**

BiancaMed was founded in 2003 and is a spin-off from U C Davis's School of Electrical, Electronic and Mechanical Engineering. The company’s ‘baby monitor’ utilizes an active radiofrequency sensor, and detects heart rate, respiratory rate and motion. Its primary application is sleep apnea detection in babies. (BiancaMed) The device has not received regulatory clearance, nor has it generated sales. The company has an issued patent for sleep apnea detection (USPTO 2010).
**Wireless2000: Product PAM3000**

Wireless 2000 is a Canadian manufacturing and product development company that specializes in medical applications of its patent pending Ultra Wideband technology. Their product PAM$^{TM}$3000 is used to monitor patient health and is placed underneath the mattress. It utilizes ultra wideband radar to detect heart rate, respiratory rate and bed occupancy. The device is intended for use in nursing homes and has received FDA 510(k) clearance (Wireless 2000).

**Corventis: AVIVO™ Mobile Patient Management (MPM) System**

Corventis is a privately held company headquartered in San Jose, California that provides wireless cardiovascular solutions by means of medical devices, telecommunication and information technologies. The AVIVO patient management system comprises a wearable component that collects the patient’s heart rate, respiratory rate, ECG, fluid status, posture, and activity data. Patient data and trends are available to physicians on the Corventis website. The company has filed over 50 patents for their technology (Corventis 2009).

**Competitive advantage: EverOn**

- EverOn uses a contact-free, reliable low cost disposable sensor.
- It detects heart rate, respiratory rate, body movement and now the added application of blood pressure monitoring.
• The EverOn technology comprises advanced signal processing that leads to accurate detection and low false alarm rates.
• It has advanced predictive fall prevention capability and pressure ulcer prevention support features
• EverOn has received FDA 510 (k) clearance and CE approval.
• The product has demonstrated successful clinical results.

3.5. Business model

3.5.1. Target market

The company’s target market is unmonitored beds in medical and surgical wards. According to a 2007 survey, total staffed beds in all U.S. registered hospitals are about 950,000 as opposed to the total 37 million admissions. In the 35 million community hospital admissions, only 800,000 patients have the advantage of staffed beds (American Hospital Association 2008). There is a demand for improved patient supervision in general medical and surgical wards with the shortage of nursing staff.

EarlySense’s immediate target market is medical and surgical units in hospitals. They plan to extend the market to long term care, intensive care and emergency services for vital signs monitoring, patient deterioration detection and pressure ulcer prevention.
3.5.2. **Customers**

EarlySense will sell their patient supervision systems to hospitals. The systems will be incorporated in general medical/ surgical units and will be used to continuously monitor the patients and alert physicians and nurses upon deterioration.

3.5.3. **Intellectual property**

EarlySense holds two issued US patents for its technology. US Patent 7,077,810, issued in 2006, describes a method that senses the breathing pattern of the patient which helps in predicting the onset of a clinical episode. The patent covers the utilization of contact-free and mechanical sensors to predict asthma, chronic obstructive pulmonary disease, CHF, Epilepsy and Cystic fibrosis based on respiratory rate patterns (Lange, et al. 2006).


Apart from the two issued patents, EarlySense has submitted 32 patent applications worldwide that cover sensor design, algorithms for heart rate and respiratory rate detection, advanced motion analysis, fall prevention, pressure
ulcer protocol support, blood pressure change detection, false alarm reduction algorithms and multi sensor analysis.

### 3.5.4. Regulatory status

EarlySense has received 510(k) clearance for its patient supervision system. A 510(k) submission is made to the FDA when the device in question is considered as safe and as effective as an equivalent device legally marketed. The equivalent device is referred to as a ‘predicate’ device. A device that qualifies for 510(k) clearance is not subject to a pre-market approval (U.S. Food and Drug Administration 2009).

EverOn is also CE approved. The CE mark signifies that a product has met the safety, health and environmental standards of the European Economic Area. To obtain CE approval, the manufacturer has to prove that the product has passed quality assurance tests by appointing a qualified third party to perform tests.

### 3.5.5. Clinical trials

Clinical trials were conducted in three medical centers to study the monitoring ability of EverOn for its basic application. The centers include the MetroWest Medical Center, Massachusetts in the United States and Sheba Medical Center, Tel-Hashomer and Sapir Medical Center, Kfar Saba in Israel. A total of 204 patients (99 males and 105 females) were continuously monitored for over 14,000 cumulative hours. Worsening of clinical conditions which led to interventions
occurred in 29 patients (14%), with a total of 35 events of deterioration. Signs of worsening could be detected by monitoring of heart or respiratory rates (alerts and trends) as provided by EverOn in 31 of these events (88.6%). Of the 35 total events, 11 were defined as major. EverOn detected signs of worsening in 100% of these major events. At the MetroWest Medical Center, nurses were requested to validate the system alerts based on their clinical judgment. Analysis of their validation revealed one false alert of the EverOn system per 80 hours (3.4 days) of monitoring.

Case study at Sapir Medical Center

An 82 year old male was hospitalized due to pneumonia. The patient’s pacemaker was tuned at 60 beats per minute. Abnormal changes in heart rate were seen indicating that the pacemaker required to be fixed.
Evaluation of clinical studies at Metro West Medical Center

60 patients were studied and the following observations were made:

- Heart Rate and Respiratory rate readings were detected 91% of the time increasing to 96% at night
- A very low false alarm rate of 0.01 alarms per hour was seen.
- Good nurse satisfaction
- Short training period of ~30 minutes
- ~90% sensitivity to pressure ulcers
Initial feasibility studies for the blood pressure application, conducted by the EarlySense team in Israel, indicated that EverOn can be extended to continuous blood pressure monitoring. Adding this application will provide the ability to continuously guard a patient’s cardiac status.

### 3.5.6. Reimbursement

Patient monitoring systems fall under the category of Diagnosis Related Groups (DRG) reimbursement. Hospitals do not get separate reimbursement for purchasing these products. They are reimbursed fixed amounts, decided prior to hospital services, and are paid that amount irrespective of the actual costs incurred by hospitals. Hospitals are free to realize profit from the difference between the two amounts. As reimbursement is fixed, hospitals try to minimize unnecessary expenses and ensure effective resource utilization. Procedural reimbursement discourages hospitals from investing in new equipment or devices unless they are reimbursed per Current Procedural Terminology (CPT) codes which pay for the device separately. Due to stringent reimbursement policies, EarlySense may face a setback with their monitoring system. Hospitals will not be willing to invest in a patient supervision system unless it is paid for (Hsiao, et al. 1986).
3.5.7. **Implementation of business model**

Upon implementation, EverOn will enhance quality of patient supervision in medical and surgical wards, reduce preventable transfers to ICU, shorten length of patient stay and improve productivity of nurses. As estimated by the company, hospital costs per patient increase considerably with the occurrence of adverse events. Hospitals do not receive additional reimbursement for providing longer and enhanced patient care than planned upon admission. The EverOn device will lead to savings of hundreds of dollars for the hospital per admitted patient.

**Pricing**

The target pricing is intended to reduce initial capital investment barriers for hospitals while continuously generating revenue for the company. The bed-side unit is priced at $3,500 and the sensors (including annual replacements and service contracts) are priced at $1,200. The expected income per bed for the first year is ~$5,000 with recurring revenue of $1,200. The number of sensors per bed is expected to increase with the introduction of additional functionalities such as blood pressure monitoring. The company may retain their pricing or slightly increase it depending on capital investments made by hospitals. Their competitive pricing will attract compounded revenue growth, including new accounts, incremental beds in established accounts and recurring revenue from installed beds.
Manufacturing and production

EarlySense does not manufacture the patient supervision system and has hired a subcontractor with expertise in the area of medical devices. The company controls and directs production and ensures that the products meet regulatory and quality standards. The subcontractor is in charge of the manufacturing while the operations team within the company directs and verifies that the production meets requirement.

Funds

EarlySense has raised $11 million to date. In 2004, the company raised $1 million Series A funding, followed by $4 million Series B funding in 2006. An additional $6 million was raised through internal financing rounds between 2007 and 2009. In July of 2009, the company obtained non-dilutive funding from the Global Cardiovascular Innovation Center led by the Cleveland Clinic. They received $441,000 for extending the applications of EverOn to continuous blood pressure monitoring and cardiac arrhythmias.
3.5.8. Market strategy

EarlySense’s steps into the market should include a powerful market message, a strategic partnership with a well known hospital and a creative sales approach.

Market message - Emphasis on hospital savings

EarlySense should lay emphasis on EverOn’s capability to increase hospital savings by detecting preventable complications.

<table>
<thead>
<tr>
<th>Event</th>
<th>Cost per episode</th>
<th>Rate of incidence</th>
<th>Assumption</th>
<th>Total savings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiopulmonary Resuscitation</td>
<td>$43,000</td>
<td>0.5%</td>
<td>EverOn detects 50% of all episodes</td>
<td>$108</td>
</tr>
<tr>
<td>Delayed transfer to ICU</td>
<td>$34,000</td>
<td>0.2%</td>
<td></td>
<td>$34</td>
</tr>
<tr>
<td>Bed sitter</td>
<td>$2,100</td>
<td>2.0%</td>
<td></td>
<td>$21</td>
</tr>
<tr>
<td>Pressure ulcers</td>
<td>$10,845</td>
<td>1.2%</td>
<td></td>
<td>$65</td>
</tr>
<tr>
<td>Patient stay</td>
<td>$1000/ day</td>
<td>Reduction of 10% in length of stay</td>
<td>$100</td>
<td></td>
</tr>
</tbody>
</table>

Net savings by EverOn per patient admission $328

Patients per bed per year 63

Savings per bed per year $20,637

1 (Buist MD 1999 )
2 (Berger and Kelley 1994)
3 (Young, et al. 2003)
4 (HealthGrades, Inc. 2009)
5 Assuming an average length of stay of four days and 69% occupancy

Hospitals can save approximately $21,000 per bed annually with an initial investment of $4,700 in EverOn. They will also be following the increased emphasis on patient safety by regulatory agencies.
Strategic partnership with a large hospitals system

The company should leverage a strategic customer agreement with a large hospital system to generate initial sales. Currently, clinical trials are being conducted at Catholic Healthcare West (CHW), which is the eighth largest hospital system in the United States. EarlySense should convert their association with Catholic Healthcare into a lucrative partnership. With the successful conclusion of the trials, the company should ensure the installation of EverOn in patient beds.

Creative sales approach

Since hospitals are averse to capital expenditure at present, EarlySense should rent or lease out their equipment to generate initial revenue. By doing so, they can convince hospitals about the value and potential of their device and ensure future sales. Sales can also be scaled up by a marketing partnership with a top supplier of hospital equipment. This could facilitate synergistic product offering.

3.5.9. Timeline

In the second half of 2009, EarlySense achieved its objectives of establishing reference with a leading US hospital system (CHW). They have completed evaluation and initial sales in Europe and have also successfully conducted clinical trials to assess the functionality of the patient supervision system.
In 2010, the company intends to scale up sales by setting up a strategic partnership with a significant hospital system. They also plan to utilize additional distribution channels in Europe.

In 2011, the expanded product line that includes contact-free blood pressure detection and advanced respiratory monitoring will enter the market. The new device should be incorporated in cardiac step down units which are intermediate care units between intensive care and general wards. They will comprise patients who have suffered cardiac complications and will require constant blood pressure monitoring along with other vital parameters.

4. Business analysis

4.1. EverOn Value

Increases hospital savings

Poor patient supervision in general medical and surgical wards will lead to patient complications and hospital costs. On an average, the nurse to patient ratios in general medical and surgical wards is about 1:5 (Aiken, et al. 2002). According to a HealthGrades study, it was reported that ~100,000 in-hospital deaths occurred in patients who displayed patient safety indicators. Fifteen patient safety indicators were developed by The Agency for Healthcare Research and Quality (AHRQ) based on the Institute of Medicine’s definition of patient safety which is “freedom from accidental injury due to medical care or medical errors.” Seven indicators including pressure
ulcers, post-operative respiratory failure, post-operative pulmonary embolism, deep vein thrombosis and post-operative sepsis accounted for ~85% of the total 900,000 patient safety events. Failure to rescue, pressure ulcers, post-operative sepsis and post-operative respiratory failure had the highest rates of incidence (HealthGrades, Inc. 2009). Failure to rescue is failure to prevent a patient deterioration that occurs as a result of adverse events such as hospital-acquired infections, cardiac arrest or shock. (U.S. Department of Health and Human Services n.d.) There were about 500,000 hospitalizations due to primary and secondary diagnoses of pressure ulcers in 2006. 1 in 25 admissions died with a primary diagnosis of pressure ulcer while 1 in 8 died with secondary diagnosis. Pressure ulcer hospitalizations are expected to last 5 days with an average cost of $10,000 but in reality length of stay can be up to 14 days with costs of up to $20,000.

<table>
<thead>
<tr>
<th>Patient safety Indicator (PSI)</th>
<th>Incidence rate per 1000 at-risk hospitalizations</th>
<th>Excess cost attributable to the PSI ($ Billion)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure to rescue</td>
<td>96</td>
<td>N/A*</td>
</tr>
<tr>
<td>Pressure ulcer (bed sores)</td>
<td>32</td>
<td>2.41</td>
</tr>
<tr>
<td>Post-operative respiratory failure</td>
<td>17</td>
<td>1.82</td>
</tr>
</tbody>
</table>

* Patients who died due to the PSI were excluded from the excess cost calculations

Total cost that can be attributed to all 15 PSI between 2005 and 2007 is ~$7 billion.

Pressure ulcers and post operative respiratory failure accounted for about 60% of the
total cost. (HealthGrades, Inc. 2009). The EverOn continuous patient supervision system will detect timely patient deterioration and help hospitals avoid these preventable expenditures.

**Addition of blood pressure application**

**Clinical value**

The EWSS includes respiratory rate, heart rate and blood pressure as three of the five indicators required to alert hospital staff for patient deterioration. EverOn already includes respiratory and heart rates in its measurement. With the addition of the blood pressure parameter, the system is complete and can be used for early identification of patient complications. Moreover, this application will reduce the workload on nurses as blood pressure is monitored every four hours in general ward patients.

Hospitals have adopted ‘Rapid Response Systems’ to provide immediate care in life threatening situations. The criteria for alerting these teams are:

- Heart rate: < 40 or > 130 beats per minute
- **Systolic blood pressure: < 90 mmHg**
- Respiratory rate < 8 or > 28 per min
- Acute change in saturation < 90 percent despite O2
- Acute change in conscious state
- Urinary output: < 50 ml in 4 hours (Institute for Healthcare Improvement n.d.)

EverOn will help measure the parameters required to alert the rapid response teams.
**Business value:**

Blood pressure monitoring will be an add-on application to the device. Hospitals need not invest in multiple devices when a single device can monitor multiple parameters.

### 4.2. Key issues and risks

**Adoption of technology by hospitals**

EarlySense’s initial target market is general medical wards in hospitals. Despite successful clinical trials demonstrated by EverOn, hospitals in the present economic recession are averse to capital expenditures. EarlySense has to convince hospitals to adopt their technology by laying emphasis on EverOn’s savings in preventable complications. Moreover, the patient monitoring market in general wards is relatively new. New markets come with new and unforeseeable challenges that discourage technology adoption.

**Recession in the economy**

Again, this will discourage hospitals from investing in new equipment and patient monitoring techniques. They are averse to buying new devices because of the capital expenditure involved. EarlySense should come up with creative ways of overcoming this capital barrier. They can rent or lease their equipment to hospitals.

**Competition**

There are similar products entering the market. Hoana and Emfit are making patient supervision systems that monitor the same vital parameters as EverOn.
4.3. **Summary**

**Technology platform - PTT as a blood pressure indicator (7)**

PTT is a technique that has been studied for non-invasive continuous blood pressure monitoring. This is a cuffless method of measurement and does not require patient compliance. An inverse relation has been established between PTT and blood pressure. So a fluctuation in blood pressure will cause a predictable variation in PTT.

However, there are certain limitations to this technique. Pulse wave forms are damped by vascular resistance. In cases of peripheral vasoconstriction, the peripheral sensor may not be able to detect the pressure pulse and is affected by motion of extremities. Also, the effect of PEP on PTT is not fully understood. While some researchers believe that PEP incorporates an additional delay to the PTT technique, others believe that pathological conditions like left ventricular dysfunction, cardiac pacemaker and vasoactive medication have an impact on PEP, making it difficult to be ignored. With the present understanding in PTT, it can be used for detecting fluctuations in blood pressure in a patient’s condition. Further studies can prove PTT to be a useful technique in absolute blood pressure measurement.

**Business**

EverOn addresses an unmet market need – staff shortage in hospitals. The device reduces the workload of overburdened nurses, improves documentation and provides the physician access to continuously monitored patient information. The patient supervision system has demonstrated successful clinical trial results and has received
FDA 510(k) Clearance and CE Approval. The technology is patented and presents a strong value proposition. With increasing emphasis on patient safety by regulatory agencies, EverOn has an immediate market opportunity. EverOn will also help hospitals save costs by avoiding preventable complications. With respect to the blood pressure monitoring application, EarlySense should conduct clinical studies and quantify the accuracy of the system’s blood pressure monitoring ability. They should pursue their strategy of a partnership with a hospital system to establish a customer base for their device. With a firm customer base, it will be convenient for introduction of a new application into the device and increase its value.
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