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**Technology Exploitation in the Field of  
Brain Computer Interface**

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## STATUTORY DECLARATION

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## Abstract

Epilepsy is an incurable disease that afflicts approximately three million Americans of all ages, and roughly 612,000 persons were living with a diagnosis of primary brain and central nervous system tumor in the US. Treatment of these diseases may require resection of targeted brain areas and thus preoperative intraoperative localization of their primary brain functions is required to preserve language and memory. Currently, the Wada test and electrocortical stimulation are the golden standard used in medical practice for lateralization and localization of these essential brain functions, respectively. However, these techniques are time consuming and costly. A promising alternative for lateralization and localization utilizes Brain-Computer-Interfaces (BCI) to map human brain functions by measuring and analyzing brain signals directly. Recently, the BCI group at the Wadsworth center has developed two novel clinical diagnostic tests based on this technology: Electroencephalography Lateralization Index test (EEG LI test) for the purpose of language lateralization and, SIGFRIED for functional brain mapping. SIGFRIED stands for “SIGnal modeling For Realtime Identification and Event Detection”, and both clinical diagnostic tests contain innovative signal processing software. These BCI system softwares have been validated at the research level, but their commercial prospects have not been explored. Because certification for commercialization is missing, it is currently not possible to obtain reimbursement for these development results. Even if these clinical diagnostic tests were approved for commercialization, this would not indicate that the medicare companies automatically reimburse these clinical diagnostic tests. The amount, which will be reimbursed by the medicare companies, plays an import rule in the success of a development result in the medical device field. The insurance companies decide independently whether a service or product is covered and they also define the amount which will be reimbursed. In summary, both the missing certification for communalization and the missing reimbursement coverage determination limit wider use of the two clinical diagnostic tests. The time and effort to acquire these two milestones are unclear as well as the tests’ market demand at this stage.

This work highlights the essential steps necessary to launch a BCI technology successfully onto the market after the technology has been validated. This theoretical analysis is applied to two case studies that address EEG LI test and SIGFRIED. These case studies include both a detailed comparison against the current gold standards and an evaluation of its cost-effectiveness. Furthermore, these case studies address their market demand, regulatory environment, and Medicare reimbursement. A detailed time line of the necessary steps to market these technologies concludes this topic.



## Kurzfassung

Ungefähr drei Millionen Amerikaner aller Altersgruppen leiden an Epilepsie und etwa 612.000 Personen sind von einem Tumor im Bereich des Gehirns betroffen. Die Behandlung derartiger Hirnschädigungen kann eine Resektion des infizierten Hirnbereiches bedeuten und somit eine Lokalisation der wichtigsten Hirnfunktionen erfordern, um wesentliche Funktionen wie Sprache und Gedächtnis zu bewahren. Gegenwärtige Standardmethoden für die Lateralisation und Lokalisation grundlegender Hirnfunktionen sind der Wada-Test sowie die direkte elektrische Stimulation des Kortex. Beide Methoden sind jedoch zeitaufwendig und teuer. Eine erfolgversprechende Alternative eröffnet die Verwendung eines sogenannten „Brain Computer Interface“ (BCI), welches elektrische Hirnsignale direkt misst und analysiert, um die Hirnfunktionen zu detektieren. Die BCI-Forschergruppe am Wadsworth Center in Albany, New York, hat vor kurzem zwei klinische Diagnostiktests basierend auf dieser Technologie entwickelt.

Diese BCI-Software ist zwar für Forschungszwecke zugelassen, ihre kommerziellen Erfolgsaussichten sind jedoch noch nicht erhoben. Weil diese Innovationen nicht für kommerzielle Verwendungen zertifiziert sind, können sie von den Versicherungen nicht rückerstattet werden. Selbst wenn die Innovationen für kommerzielle Verwendung geprüft sind, bedeutet das nicht, dass sie automatisch von den Versicherungen rückerstattet werden. Diese entscheiden eigenständig, ob eine Behandlung rückerstattet wird sowie über die Höhe des Betrages. Die fehlende Zertifizierung und Rückerstattungsentscheidung limitieren somit eine weit verbreitete Verwendung dieser Diagnostiktests. Der Zeitaufwand und die Kosten, um diese Zertifizierungen zu bekommen wie auch die Marktnachfrage sind gegenwärtig nicht bekannt.

Diese Arbeit beschreibt die notwendigen Schritte, um eine auf BCI-Technologiebasierende Software auf dem Markt zu platzieren, nachdem ihre Funktionstauglichkeit nachgewiesen wurde. Die erforderlichen Schritte umfassen die Ermittlung der Marktnachfrage, die Klärung der notwendigen Zertifizierung und Beschreibung der Rückerstattungsrichtlinien von den Versicherungsanstalten. Das theoretische Wissen wird auf die zwei Fallbeispiele angewandt. Diese Fallstudien beinhalten einen detaillierten Vergleich mit der jeweiligen etablierten Methode sowie eine Bewertung ihrer Wirtschaftlichkeit. Resultierend aus diesen Erkenntnissen werden der Zeitablauf sowie die Kosten der benötigten Schritte, um diese Technologien auf den Markt zu bringen, dargestellt. Die Wirtschaftlichkeitsanalyse ergibt, dass diese ein großes Kostensenkungspotenzial für die Krankenhäuser haben, weil die Durchführungszeit und der Personalaufwand im Vergleich zu den etablierten Methoden deutlich geringer sind.

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# 1 Introduction

A Brain-Computer Interface (BCI) is a special human-machine interface that allows a connection between the brain and a computer without any activity from the peripheral nervous system. Instead, a BCI records the electrical activity either non-invasively from the surface of the scalp, or invasively with the help of implanted electrodes. While numerous different BCI systems have been validated for many purposes, BCIs typically required a major development effort to create and test the customized software for each specific application and user. Recently, this problem has been solved with a software platform called BCI2000, discussed below. Concurrently, advances in electrode technology, electronics, signal processing, and other fields have paved the way for new BCI applications for new user groups.

As a result, the very definition of “BCI” is expanding. While conventional articles define a BCI as a device used strictly for communication Wolpaw et al. (2002), new articles have expanded the definition to include a broader range of passive monitoring devices and medical applications. Similarly, various research articles and new products reflect the growing enthusiasm and opportunity surrounding BCI systems.

**BCIs for healthy users** Several different market segments are interested in this new technology. Neuromarketing has received a lot of attention in the popular media Lewis and Brigder (2005). As the name implies, neuromarketing involves advanced analysis of customer behavior based partly on brain imaging technologies like electroencephalography (EEG) and functional magnetic resonance imaging (fMRI). One of the most popular studies in this field was done by the group of Read Montague. They evaluated the differences in consumer responses to either Coke and Pepsi McClure et al. (2004). New BCI products are also being sold within the gaming industry.

The company Neurosky released their MindSet BCI system in 2009. This package includes a headset that records brain signals from the scalp, and these signals provide information about the users’ mental states. The famous game manufacturer Mattel also sells a BCI product based on Neurosky technology called the Star Wars Force Trainer, which allows players to move a ball via concentration. Both systems are available for

under USD100. Similar technology has been used in other games and in safety devices that track the attention of vehicle operators and warn drivers if they are falling asleep Huang et al. (2008), Müller et al. (2008).

These two systems underscore both the opportunities and challenges of developing BCIs for new user groups. Until recently, BCI users were typically “locked-in” patients, such as people in the last stage of ALS, who have no muscle control left. When developing applications for new user groups, the critical question is: why use a BCI? In the case of game or neuromarketing applications, the answer may be that the BCI provides a more entertaining or convenient means of communication. That is, the BCI provides information that might be otherwise available (such as through a joystick or questionnaires), but in a different way.

However, another reason why people might use a BCI is need. A BCI could provide information or opportunities that are not otherwise possible. In particular, if BCIs can provide a superior mechanism to diagnose or treat a disorder, then they might be particularly useful to some users, who might pay considerably more than about US\$100. Some recent research has already explored BCI systems for medical applications such as rehabilitation of movement disorders resulting from stroke or amelioration of autistic symptoms Birbaumer and Cohen (2007). We focus here on a related emerging application: BCI technology for functional brain mapping to facilitate surgery.

**BCIs for functional brain mapping** Many people with drug resistant epilepsy (i.e., epilepsy that cannot be controlled by drugs) or with brain tumors consider invasive brain surgery. In such surgery, the affected areas are surgically removed. This type of surgery is extremely effective because it reduces or eliminates seizures or tumor growth in these patients.

As part of the pre-surgical preparations, experts must identify the affected areas of the brain, as well as the areas that correspond to important functions such as motor or language function. The surgery will then maximize the amount of affected tissue that is removed while simultaneously minimizing the removal of areas important for key functions. At present, this functional mapping requires electrodes that are implanted on the surface of the brain, together with a relatively old technique called electrocortical stimulation, which is very time-consuming and has many other problems.

One of the most disconcerting risks of electrocortical stimulation is that it can induce seizures, particularly in patients who already have such severe epilepsy that they require surgery. Electrocortical stimulation is also expensive, slow, and inaccurate. All other more modern techniques, such as functional magnetic resonance imaging (fMRI), are impractical or have other severe limitations (Wolpaw et al. (2006)). Thus, they have

not replaced electrocortical stimulation, which remains the gold standard despite its severe problems.

## 1.1 Initial situation

The BCI group at the Wadsworth center has developed a new clinical diagnostic test that uses the electrodes that are already implanted in all these patients. Using modern signal processing techniques, they can detect and visualize (in real time) the brain signal changes associated with a particular function, such as when the patient speaks or moves a limb. This results in a functional mapping technique that can be accomplished in minutes. The new technology is faster as well as more accurate, and avoids some other problems with conventional techniques. "In particular, since the system relies on passive recording from electrodes that are already implanted, there is no electrocortical stimulation and hence no risk of seizure. The Wadsworth group just published a multi-center study that demonstrates the efficacy of this new clinical diagnostic test, and shows that the results generally agree with the results achieved using the present gold standard, electrocortical stimulation" cf. Brunner et al. (2009).

In a related development result, the Wadsworth group has also explored new ways to identify the brain regions responsible for language using EEG based electrodes. These noninvasive electrodes do not require surgery or significant preparation effort. The Wadsworth group's new technology can identify which hemisphere is dominant for language function. This information is important because doctors need to know where to implant electrodes; implanting an electrode grid in a non-dominant hemisphere entails unnecessary time, expense, and risk.

Hence, doctors will often apply a test called the Wada test to identify the language dominant hemisphere. This test was developed many decades ago, and also remains the gold standard despite several problems. Notably, the test requires injecting a chemical such as sodium amytal into the carotid artery to effectively shut down one brain hemisphere prior to the language test. Obviously, this is a nontrivial procedure, and can produce scarring, infections, seizures, strokes, anaphylactic reactions, and other problems Loddenkemper et al. (2004). The new approach from the Wadsworth team is completely noninvasive, requiring no invasive electrodes, drugs, or injections, and thus avoids these problems. This new approach is safe and requires much less time and expense.

## **1.2 Problem**

At this stage, it is unclear whether these two clinical diagnostic tests present an economically feasible innovation. It is unclear because no business strategy evaluating the suitability, cost-effectiveness and acceptability has been developed. The development results are certified only for research purpose and for commercial distribution, every medical device must be approved by the Food and Drug Administration (FDA). Currently the FDA approval conditions for the two diagnostic tests are unknown as well as the required documentation to apply for FDA approval.

The field of medical device has an unique character that the end-user (patient) does not pay directly for service. Instead a medicare company normally covers the expenses, hence the goal of the development results is the receive a positive Medicare coverage determination. For the two clinical diagnostic tests, the Medicare coverage decision procedure is ambiguous and also whether the innovations are valid for reimbursement. Furthermore expenditure of time and costs for the FDA approval and Medicare coverage determination is not evaluated yet. Also the appraisal of the development results' market demand is missing, which is one of the most imported factors to evaluate the feasibility. This inhibits the venture of commercializing these new clinical diagnostic tests.

## **1.3 Aim**

The mentioned novel diagnostic techniques exist currently as prototypes that are only used for research purpose. The main task of this master's thesis is to investigate the economic feasibility of these development results. Therefore, this work estimates the market demand and the effort, which are necessary for the commercialization of the new clinical diagnostic tests. In particular, the required certification and the volume of the necessary tests and documentation to obtain the certification should be clarified. Furthermore, the goal of this work is to develop a strategy to obtain Medicare reimbursement, which is an fundamental milestone of medical device innovation. The interest of every Medicare company is to reimburse the most cost-effective treatment and one object of this work is to address this issue. The interest of a manufacturer is to sell the clinical diagnostic tests and hence this work points out the purchasing decision impact factors of customer (hospital).

The final outcome of this work should be a time line and cost estimation that includes all necessary step of the clinical diagnostic tests pre-commercial development.

## 1.4 BCI2000

“BCI2000 is a general-purpose research and development platform that greatly facilitates implementation, evaluation, and comparison of different BCI options” Schalk et al. (2004). BCI2000 has been in development for over 10 years and it has clearly emerged as the dominant software platform in BCI research. Over 450 labs have downloaded it, and it has been referenced in very many articles Schalk (2009). The Wadsworth group has received multiple grants to support further development of BCI2000, which not only improved the software itself, but also fostered BCI2000 support mechanisms such as workshops, conference talks, published articles, and a website with helpful instructions and other documentation. Indeed, the work described in this master’s thesis is based on BCI2000, and would not have been possible otherwise without substantially more effort.

Fig. 1.1 illustrates the basic modular structure of BCI2000. The four modules (Oper-

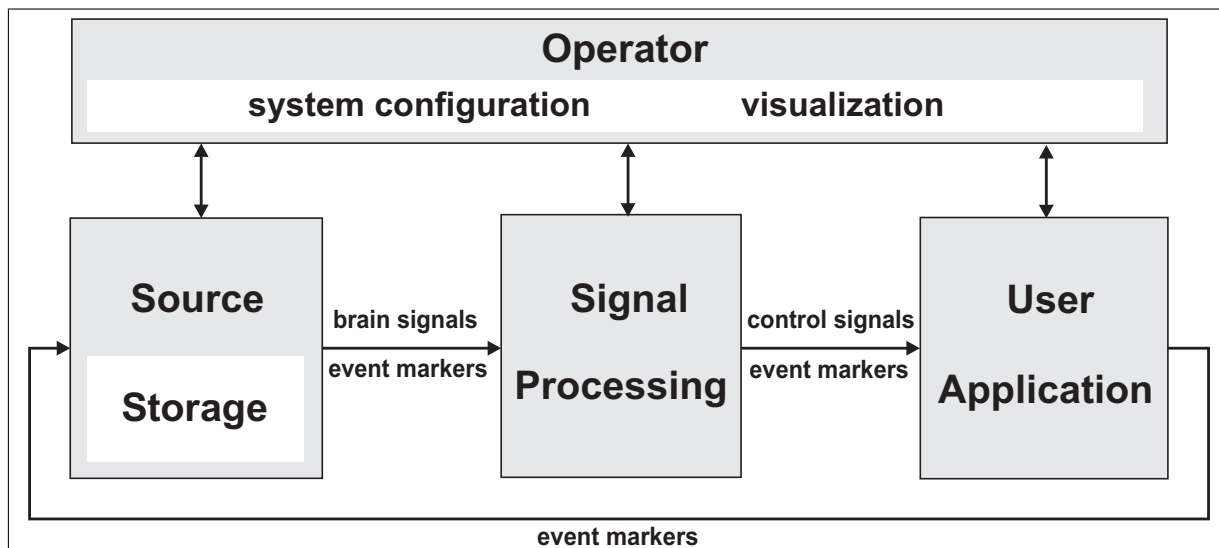


Figure 1.1: BCI2000 design. “The four modules in BCI2000 are called Operator, Source, Signal Processing, and Application” cf. Schalk et al. (2004).

ator, Source, Signal Processing and Application) correspond to the four components of a BCI. These four modules communicate using TCP/IP sockets, and thus can be placed on different machines or even in different locations. The central configuration is provided by the Operator module. The interfaces are well defined and thus each module is interchangeable. One goal of this thesis was to provide a SIGFRIED signal processing module for BCI2000.

BCI2000 was developed primarily by Gerwin Schalk at the Wadsworth group. While many people have contributed as well, the software is patented and owned by the Wadsworth group, and thus is protected against infringement.



## 1.5 BCI2000 group at Wadsworth Center

Our team is part of the Wadsworth Center. The Wadsworth Center is a comprehensive state public health laboratory that is unique among state public health laboratories for its commitment to basic and applied biomedical and environmental research. The Wadsworth Center has a staff of 1,100 (including more than 175 doctoral-level scientists) and is housed in 900,000 square feet of state-of-the-art facilities. It maintains a number of core facilities for all investigators, including a core of specialized research facilities for state-of-the-art microscopy, advanced biochemical techniques, molecular neuroscience, and nanofabrication of devices, as well as an AAALAC-accredited animal facility, a computer support center, and a large biomedical library. Wadsworth investigators receive substantial research funding (i.e., >\$35m in 2006) from outside research sponsors.

The BCI research group, headed by Jon Wolpaw, has grown so much over the past few years that it has been subdivided, with different research teams focusing on different challenges. One of the research teams, headed by Prof. Dr. Schalk, focuses on developing BCI2000.

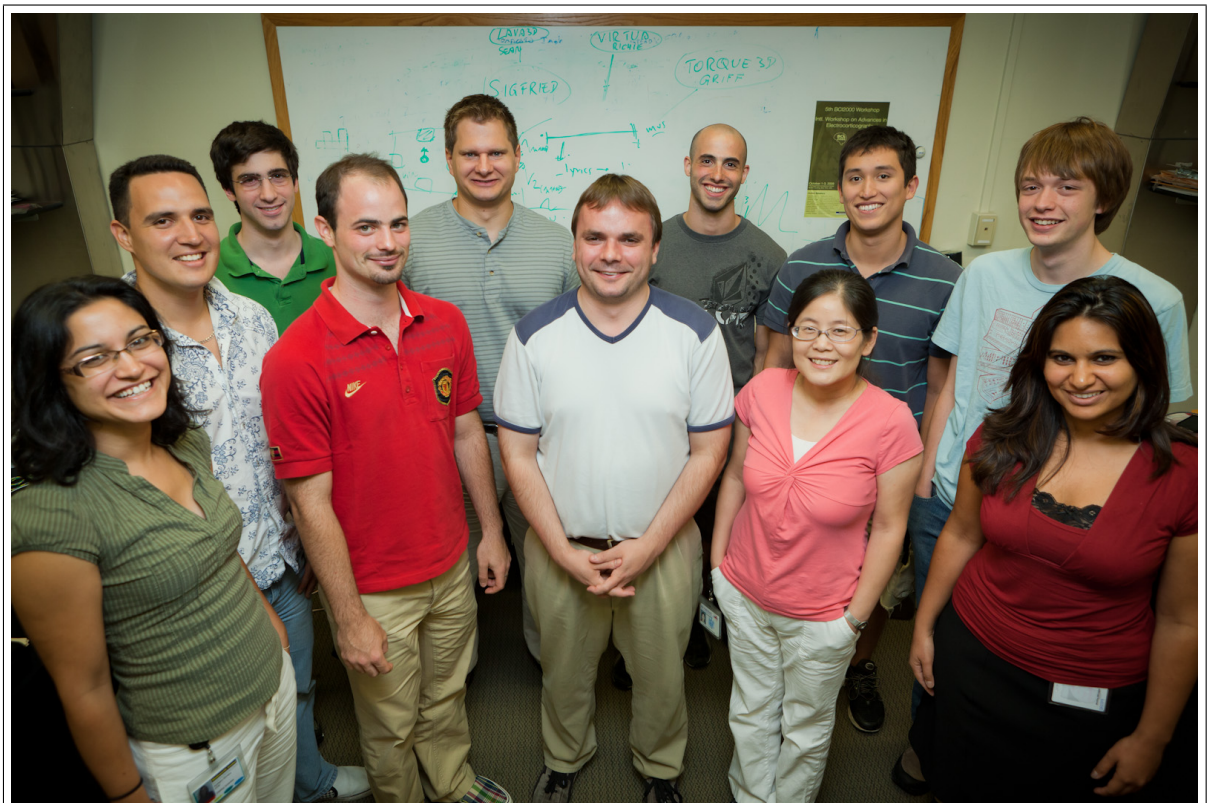


Figure 1.2: BCI2000 group at the Wadsworth Center.

While Schalk and other colleagues also conduct experimental research involving

both invasive and non-invasive systems, their primary focus is on improving BCI2000 and its applicability to new paradigms, with a strong emphasis on the functional brain mapping paradigms described in this thesis. The functional principle of the BCI at the Laboratory of Nervous System Disorders at the Wadsworth Center in Albany, NY is illustrated in Fig. 2.1. Early Wadsworth BCIs (see Wolpaw et al. (1991) and Wolpaw and McFarland (1994) for a comprehensive review) relied on noninvasive imaging tools. Our team at Wadsworth began exploring ECoG based BCIs several years ago, and adapted BCI2000 and other tools accordingly.

## **1.6 Procedure and document structure**

Chapter I introduces Brain-Computer Interfaces (BCI) and explains the work of the BCI group at the Wadsworth Center in detail. It provides a short introduction to current BCI applications and BCI2000.

Chapter II extends our review of the state of the art with an overview of basic neuroscience, functional brain mapping technologies, and relevant application fields.

Chapter III details the two recently developed clinical diagnostic tests described in this thesis, including an analysis of cost effectiveness relative to conventional methods and technologies.

Chapter IV assesses the market demand for the two clinical diagnostic tests based on existing marketing studies.

Chapter V explains the regulatory environment for the two development results with a focus on the Food and Drug Administration (FDA) approval process. The FDA plays a major role in the certification process of a medical device in the US.

Chapter VI describes the reimbursement process between the hospitals and insurance companies, because in the medical device market, the end user (the patient) does not usually pay directly for the treatment. Instead, the patient's insurance reimburses the hospital and also decides how much money can be reimbursed.

Chapter VII reviews the purchasing-decision process between the innovation's manufacturer and the hospital. The purchasing process is the last step at the innovation process and, obviously, it is the overall goal of the manufacturer.

Chapter VIII presents a conclusion, including a time line and further directions.

## 2 Background

This chapter provides a general overview about BCI Systems, functional brain mapping and language lateralization because the innovative clinical diagnostic tests, which are introduced in chapter development results at the Wadsworth Center, are novel techniques for functional brain mapping and language lateralization. Thus this chapter lists the different methods for both functional brain mapping and language lateralization. The current established method for functional brain mapping, Electrocortical stimulation, and the gold standard for language lateralization, Wada test, are explained particularly in order to compare them against the recently developed clinical diagnostic tests in chapter 3. The two application fields of the development results, epilepsy- and brain tumor, are explicated in the end of this part.

### 2.1 BCI systems

Brain-Computer Interfaces (BCI) use Electroencephalography (EEG) or other neurophysiological methods to extract specific features of brain activity (e.g., sensorimotor rhythms, slow cortical potentials, event-related potentials) and translate them into an output signal that can be regulated by the specific user. All BCI systems require four processes, as shown in 2.1. First of all, brain activity is recorded, which is called Signal Acquisition. Next, a Signal Processing module must categorize the user's brain activity after learning the individual's subjective signal features. Third, the user's brain activity must produce some effect in real-time, such as moving a cursor or wheelchair. Finally, the BCI must provide some feedback as part as an overall operating system that controls how the different modules interact with each other and with the user Wolpaw et al. (2002).

In the case of a conventional BCI - a device for communication and control - the user receives real-time feedback. As noted above, this thesis addresses a new type of BCI in which the goal is not to provide communication, but rather to provide functional brain mapping. Hence, the user does not receive any real-time feedback. Instead, real-time feedback is sent to the operator, who can use the information to learn more about the

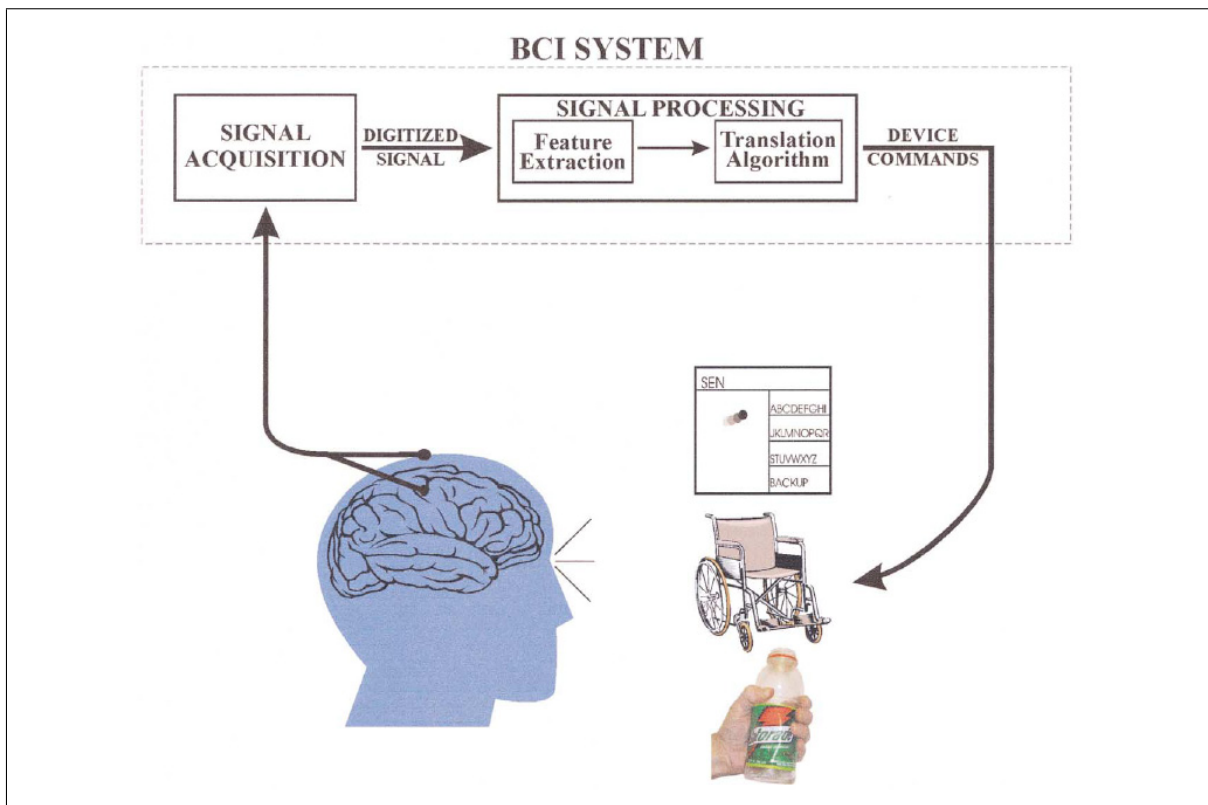


Figure 2.1: BCI components. “Basic design and operation of any BCI system. All BCIs have four components: Signal Acquisition (measuring brain activity); Signal Processing (translating brain activity into outputs); Device Commands (executing the desired commands); and an Operating Protocol (communication among modules and the user)” Wolpaw et al. (2002).

patient’s brain. Otherwise, the system described here is identical to a conventional BCI - all four processes are necessary and rely on very similar hardware and software.

### 2.1.1 Signal acquisition

There are many ways to study brain function in real-time. The different brain imaging approaches used in BCIs are generally divided into two categories: invasive and non-invasive. Invasive techniques require a neurosurgical procedure to implant electrodes on or in the brain. Non-invasive techniques rely on electrodes placed outside the head, often in an electrode cap, and thus do not require surgery, drugs, injections, or other invasive procedures.

**Non-invasive:** Over 85% of BCIs rely on non-invasive methods (Mason et al., 2007). Brain activity can be detected outside of the scalp with different technologies. The most common non-invasive neuroimaging technology is the electroencephalogram (EEG), shown in Figure 2.2 on page 10 (A). This is a measure of the electrical activity over

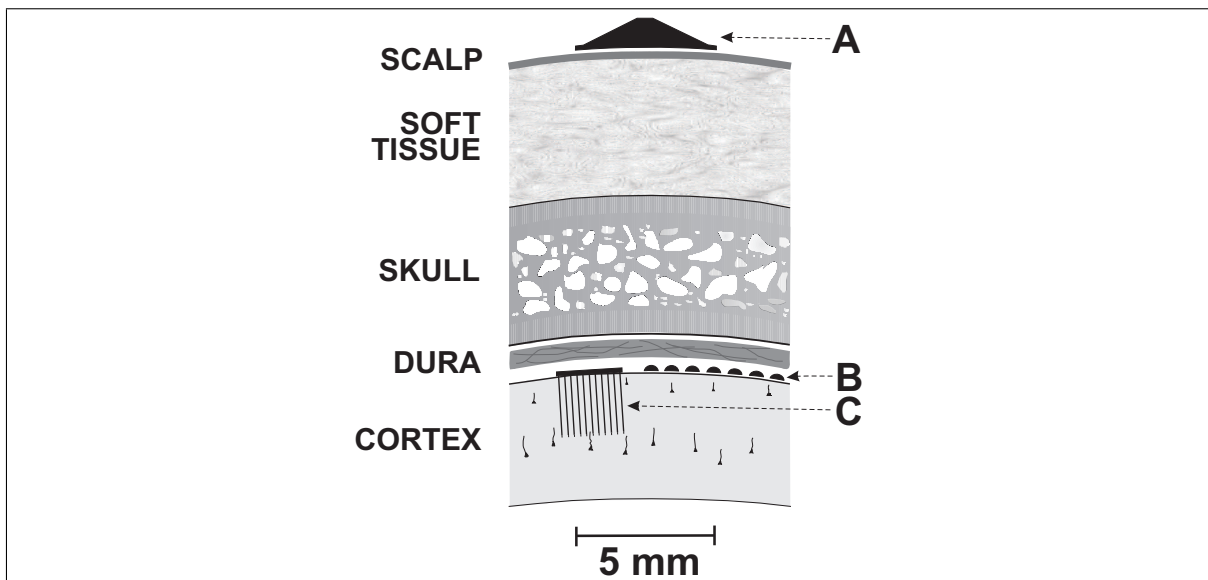


Figure 2.2: BCI sensor types. “BCIs may rely on invasive or non-invasive electrodes. (A) shows a non-invasive electrode placed outside the scalp. (B) and (C) show two types of non-invasive electrodes. Electrodes may be placed on the surface of the brain (B), or may penetrate the brain (C)” Brunner (2005).

a certain area of the brain. While non-invasive electrodes do not provide as much information as invasive electrodes, they are adequate for many purposes, including identifying the language dominant hemisphere.

**Invasive:** Invasive electrodes are subdivided into two categories. Some electrodes, called ECoG electrodes, measure the electrocorticogram, which reflect’s the activity on the surface of the brain. These electrodes do need to be surgically implanted, but entail less risk and damage because they never penetrate the brain (see part (B) of Figure 2.2 on page 10. Other depth electrodes do penetrate the brain’s surface (see part (C) of Figure 2.2 on page 10. Since these different types of electrodes provide different information, they are better suited to different BCIs. The invasive approach described in this thesis relies on ECoG electrodes.

Invasive methods have obvious drawbacks, including the added time, cost, risk, and ethical issues inherent in neurosurgery. However, invasive electrodes can provide a more detailed picture of brain activity, with less interference from external noise sources. Invasive BCIs are also always available. That is, there is no need to prepare the subject for each session of BCI use, nor to wash electrodes afterward. The consensus of most BCI researchers is that neither approach is generally superior; the choice of neuroimaging technology depends on each subject’s situation and needs.

## **2.1.2 Signal processing**

One of the most heavily researched facets of BCIs is Signal Processing. Many different linear and nonlinear approaches have been used. In addition, various preprocessing techniques are common, such as improved spatial filters Krusienski et al. (2008) or dimensionality reduction techniques. Hence, this master's thesis does not focus heavily on development of new signal processing algorithms, as they have been well explored, and additional research is unlikely to yield a major breakthrough.

## **2.1.3 Device command**

Early BCIs were used to control simple monitor based applications such as spellers Farwell and Donchin (1988), Wolpaw et al. (1991). More recent work showed that BCIs could control many other devices, such as a wheelchair, mobile robot, or orthosis Millán et al. (2010), Pfurtscheller et al. (2010). This component of a BCI is not emphasized here, since this thesis does not focus on conventional BCIs for communication and control.

## **2.1.4 Operating environment**

Any BCI requires an operating environment. The operating environment might specify details such as how the modules pass information to each other, how to present feedback, and how to handle errors. Until fairly recently, this was a major challenge in the BCI field. Many groups developed their own operating environments, which entailed many problems. An accurate real-time EEG data collection and analysis system is hard to develop, even for groups with a very strong computer science background, leading to some failed projects and other problems Bayliss, Inverso and Tentler (2004). In the past few years, some groups have proposed or tried to develop some kind of universal platform that any group could use as a BCI operating system. For example, the OpenVibe system from the INRIA group in France is publicly available, and has been downloaded by some groups. However, the most trenchant and widely used program is called BCI2000, discussed below.

## **2.2 Functional brain mapping**

This chapter introduces the different methods for functional brain mapping and in particular it explains language lateralization. The term functional brain mapping can be defined as, "the attempt to specify in as much detail as possible the localization of

function in the human brain” Savoy (2001). This chapter starts with a short description of the biological structure of the human brain followed by functional brain mapping’s historical development and an overview of the established methods for language lateralization and functional brain mapping.

The human brain is a very complex organ as well as the central command unit for the nervous system. If you take a look at a human brain, you can recognize three different areas:

- 1 Cerebrum
- 2 Cerebellum
- 3 Metencephalon, which passes into the spinal cord

The cerebrum, the largest part of the brain, is divided in the middle into two halves called left and right hemispheres. Between the hemispheres, there is a thick nerve cord known as the corpus callosum. The cerebrum’s outer layer, which is 2–4mm thick, is called cerebral cortex or grey matter, hence every brain consists of a left and right cerebral cortex. The neurons and unmyelinated fibers in cerebral cortex have a large field of responsibility, for example language, memory and attention. Each hemisphere is divided into four lobes and Figure 2.3 on page 12 illustrates them. Each lobe

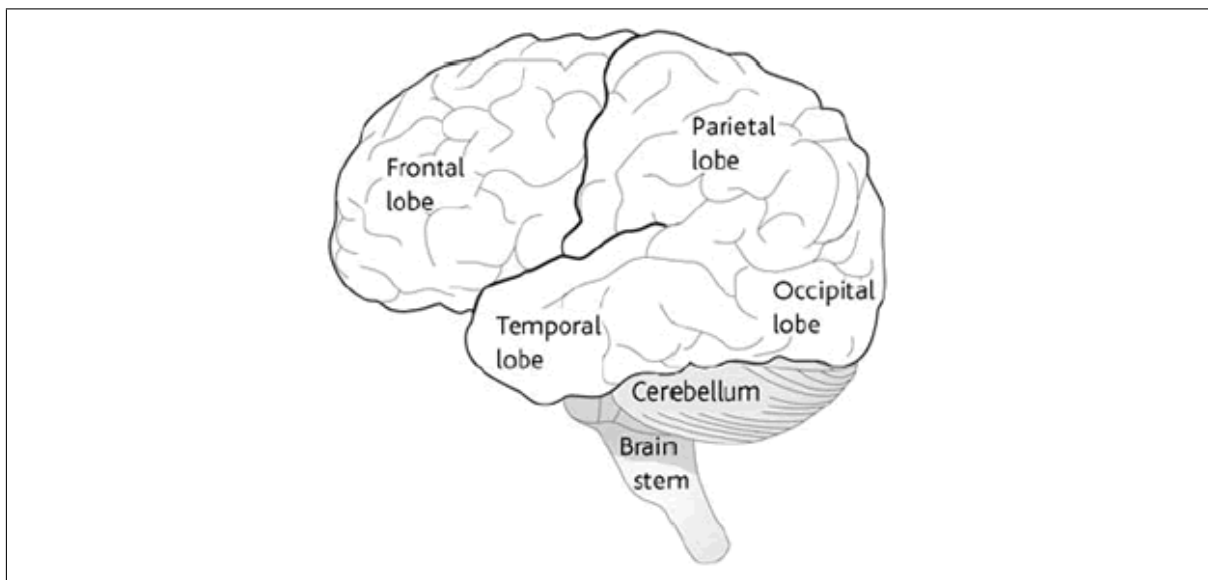


Figure 2.3: Human brain. “One hemisphere of the human brain is depicted in this figure and the hemisphere’s outer layer is called the cerebral cortex, which plays a major role in e.g., language, attention, thought and memory. The cortex of each hemisphere can be divided on the basis of gross topographical conventions into four lobes: Frontal-, Parietal-, Temporal and Occipital lobe” Macmillan Cancer Support (2009).

has specific character, which are explained below.

Frontal lobe is situated at the front of the brain and normally in authority of both language skills and motor functions. The body movements are carried out by the motor cortex, which is located in the back of the frontal lobe.

Parietal lobe is placed in the center of the brain and it processes the sensorial information like pain and touch. The body's senses are handled at the somatosensory cortex, which is a part of this lobe.

Temporal lobe is situated at the bottom of the brain and it contains the primary auditory cortex, amygdala and hippocampus. The hippocampus is responsible for long-term memory and the amygdala dominates the responses linked with arousal, fear and emotional secretions.

Occipital lobe the occipital lobe comprises the visual cortex, which processes the information from the eyes, at brain's back.

However, for many purposes it is not satisfactory to distinguish only between four lobes and many scientists have been working on methods and technology to create a more detailed map of the human brain. Still nowadays, the brain is one of the most unexplored parts of the human body and plenty of further research work is needed to understand how the human brain is working. The following section gives a historical overview on development of functional brain mapping and out if it the resultant brain function maps.

**History of functional brain mapping** In the last century the electrical stimulation was the most important method to explore and discover the different areas of the brain. The Italian scientist Luigi Galvani (1737-1798) discovered that muscles and nerves are electrically excitable around 1786. In 1802, Giovanni Aldini's experiments showed that also the human brain is electrically excitable and the next milestone was the development of the "Homunculi" map (see Figure 2.4 on page 14) by Wilder G. Penfield. With the use of electrocortical stimulation, Penfield and his group created a detailed map, that represents the localization of the different body parts on the cerebral cortex, which is known as the outermost layer of the cerebrum. During brain surgeries for the purpose of treating severe epilepsy, Penfield and his group stimulated the patient's cerebral cortex with electrical probes. Because of the use of local anesthesia, they could monitor the different response behaviors and characteristics of the patient according to the different stimulated brain areas. The "Homunculus" is still up to date and also electrocortical stimulation is the state of art for functional brain mapping.

The composition of the human brain is morphologically bisymmetric. Although this symmetry indicates a substantially similar construction, it is known from the many studies and experiments that several functions are located asymmetrically. In other words,



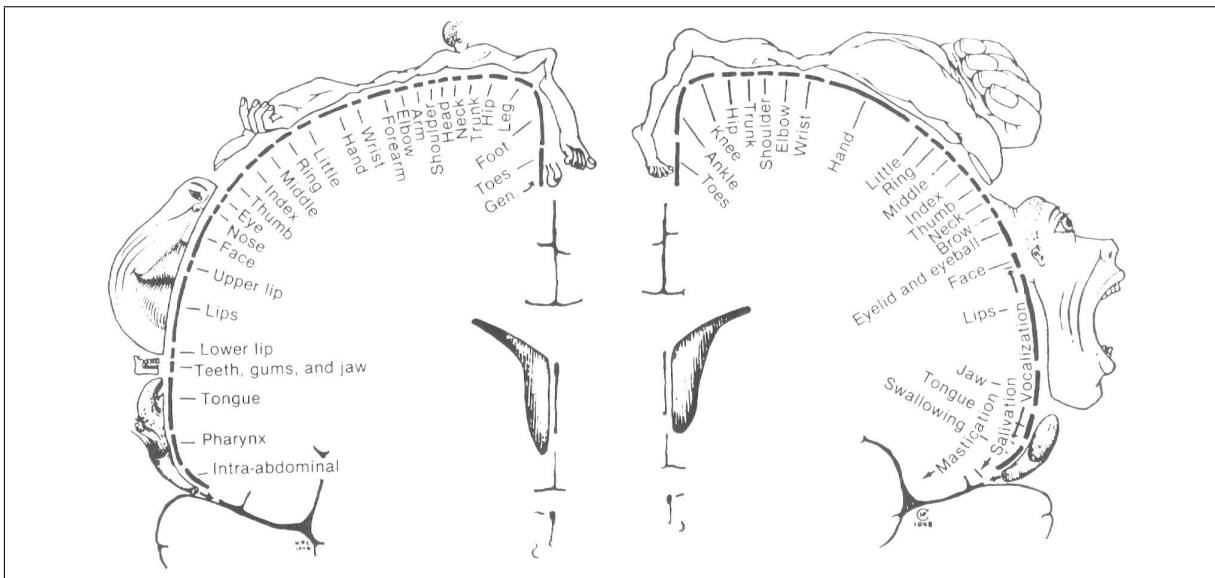


Figure 2.4: Motor homunculus. “Detailed picture of the motor strip, showing what is sometimes called the motor homunculus, which is a depiction of how motor functions are localized along the motor strip. The portion adjacent to Broca’s area controls the face and mouth” Sabbatini (2003).

some brain functions e.g., language and memory, can be found on either the left or right hemisphere and in a few cases in both hemispheres. Right handed persons have the language function normally on the left hemisphere. “The specialization of the left hemisphere for language was one of the earliest observations of brain asymmetry. Reported in the 19th century by Broca and Wernicke, language was found to be more severely impaired in response to tumors or strokes in the left hemisphere. Language production and some aspects of syntactic processing have subsequently been localized primarily to areas of the anterior left hemisphere.” Toga and Thompson (2003). Unfortunately the correlation between handedness and language lateralization, which stem from the neuroanatomical inequality, functional division, and specialization of the cerebral hemispheres, does not apply to every person. Hence different methods for language lateralization have been developed and Section 2.2.3 discuss them in detail. However, every human brain looks slightly different and thus the exact position of the brain functions are also variable from human to human. Thus it is not possible to predict the exact location of brain functions but the brain maps provide a good indicator, where a brain function is expected. Because of that it is necessary to locate the brain functions for every individual person.

## 2.2.1 Electrocortical stimulation

As the name indicated, the paper “Functional brain mapping and its applications to neurosurgery” explains the methods for functional brain mapping and content of the

next paragraph is based on this paper.

“Since the 1930s, direct electrocortical stimulation (ECS) testing has been the gold standard method for mapping brain function in preparation for surgical resection. The motor cortex is mapped intraoperatively by stimulating the pre- and postcentral gyri, as well as the premotor area and supplementary motor area. ECS for motor mapping may be performed under general anesthesia without muscle relaxants and in motor mapping, ECS is used as an activation technique. To test language functions, it is necessary that the patient remain awake and able to perform certain tasks such as counting or naming. Awake craniotomy for language mapping is typically performed using a combination of local anesthetic field block and short acting general agents to induce a rapidly reversible hypnotic state. Once the scalp, cranium, and dura are opened, the sedation is allowed to wear off so that the patient may cooperate with behavioral testing. During the cortical stimulation testing, the patient is awake and asked to perform language tests such as counting or naming while the surgeon stimulates the cortical surface. Areas in which cortical stimulation induces speech arrest or paraphasic errors are considered essential for language function. In this case, ECS is used as an inhibition technique causing disruption in normal neuronal firing. Because the bipolar stimulating electrodes have a 5-mm tip separation, a 1-cm margin is generally respected during the subsequent resection. In a study of 40 patients undergoing removal of gliomas in the dominant temporal lobe, among patients without preoperative language deficits, 87% had no deficits postoperatively using the above methods. ECS can also be performed extraoperatively. This option is used primarily for epilepsy surgery for the mapping of the seizure focus through the chronic (< 1 wk) implantation of intracranial electrodes. In addition to electrocorticography, cortical stimulation for the determination of eloquent cortex may also be performed during this time period. When indicated, this technique has the advantage of allowing significant time and a sufficiently relaxed and cooperative patient to allow detailed cognitive testing” cf. Tharin (2007).

### **2.2.2 Functional magnetic resonance imaging (fMRI)**

Functional MRI is considered an indirect method to assess brain activity, because it is based on the change of the blood oxygenation level dependent (BOLD) signal. “The fMRI techniques are based on changes in regional blood flow that occur in response to neuronal activity. Local increases in neuronal activity lead to greater blood flow to the cortical tissue parenchyma” cf. Belliveau et al. (1991).

Theoretically, functional magnetic resonance imaging can be used for functional brain mapping but in practice only determination of cerebral dominance is executed with

fMRI. “Functional MRI is noninvasive and, therefore, repeatable, both for many runs in a single session (unlike the Wada test) and on multiple occasions to follow patients over time. Because of its non-invasiveness and safety, fMRI is suitable for use in children. Unlike Wada testing, fMRI can provide localization and not merely lateralization of critical functions such as language and memory. Finally, fMRI is able to demonstrate functional activations in the depths of cortical sulci, not just at the cortical surface, an advantage over the “gold standard” electrocortical stimulation. Disadvantages of fMRI include sensitivity to motion-related artifacts, including those arising from the heartbeat, breathing, and head motion. This has proven particularly problematic for language mapping, generally precluding the use of tasks involving overt spoken language. fMRI also does not have the proven clinical track record of the Wada test” Tharin (2007).

### **2.2.3 Methods for language lateralization**

The article *“An Update on determination of language dominance in screening for epilepsy surgery: the Wada test and new noninvasive alternatives”* Abou-Khalil (2007b) gives a great detailed overview about all methods. The paper’s conclusion is that “Several methods provide sufficiently good lateralization of language dominance that they could be considered alternatives to the Wada test. It is likely that fMRI will be the most widely used method, obviating the need for the Wada test in the majority of patients with clearly lateralized language. However, the best testing paradigm and the best method of image analysis still have to be defined” Abou-Khalil (2007a). The Table 2.1 evaluates all methods for language lateralization and based on the conclusion, we picked the Wada test and functional MRI as the current methods used for language lateralization.

#### **Wada test**

“Most epilepsy patients considering a surgery undergo the Wada test. This test is officially known as the intracarotid sodium amobarbital procedure (ISAP), but the nickname Wada test is commonly used. The name comes from the physician who first performed it, Dr. Juhn Wada” Weiner (2004). “Juhn Wada introduced the intracarotid amobarbital procedure to lateralize language in 1949, and soon thereafter, Brenda Milner included memory testing during the procedure to help determine risk for postoperative amnesia” Meador and Loring (2005). Since developed in 1949, the Wada test is the gold standard for language and memory lateralization. The next two subsections elucidate the procedure and involved doctors of the ISAP.

Method	Physiologic basis	Directness of measurement	Reliability relative to Wada test	Availability
Wada test	Deactivation by anesthesia	Direct	NA	++
Dichotic listening and divided visual field test	Directness of access to language cortex	Indirect	++	+++
rTMS	Deactivation by electrical interference	Direct	++	+
sMRI	Association with dominance	Very indirect	+	+++
ERP	Electrophysiologic expression of activation	Direct	+	+++
MEG	Magnetic flux directly associated with activation	Direct	+++	+
fTCD	Hemodynamic response to activation	Indirect	+++	+++
NIRS	Increased oxygenation	Indirect	+++	++
PET	Hemodynamic response to activation	Indirect	+++	+
SPECT	Hemodynamic response to activation	Indirect	++	+++
fMRI	Increased oxygenation	Indirect	+++	+++

ERP: event-related potentials; fMRI: functional MRI; fTCD: functional transcranial Doppler; MEG: magnetoencephalography  
NIRS: near infrared spectroscopy; PET: positron emission tomography; rTMS: repetitive transcranial magnetic stimulation;  
sMRI: structural MRI; SPECT: single photon emission computed tomography.

Table 2.1: Methods for determining cerebral dominance. “It is worth noticing that the Wada test is the only invasive method but the current gold standard for language and memory lateralization. The comparison concludes that fMRI is the most promising emerging technology for determining cerebral dominance” cf. Abou-Khalil (2007b).

**Involved doctors and required equipment** The Wada test procedure usually demands three doctors: Neuroradiologist, Epileptologist and Neuropsychologist.

**Neuroradiologist** deals with the radioactive substances and imaging devices and his task during the test is to study the patient’s brain structure. However, a Radiology resident must run through four months of learning neuroradiology to get a radiology board certification in the United States. The following fellowship program takes one or two years and then an additional one or two years of training are required for interventional neuroradiology.

**Epileptologist** has special training in treating epilepsy patients, especially in the cases with difficult controllable seizures. They also are also experts in handling children and pregnant women with epilepsy. Their special training starts with three years of residency in Pediatrics after medical school and then a fellowship in Pediatric

Neurology comes after that. The last part of the training are two years of particular concentration on pediatric epilepsy.

**Neuropsychologist** “A clinical neuropsychologist is a professional within the field of psychology with special expertise in the applied science of brain-behavior relationships. The clinical neuropsychologist uses psychological, neurological, cognitive, behavioral, and physiological tests to evaluate a patient’s neurocognitive, behavioral, and emotional strengths and weaknesses and their relationship to normal and abnormal central nervous system functioning. The clinical neuropsychologist uses this information and information provided by other medical/healthcare providers to identify and diagnose neurobehavioral disorders, and plan and implement intervention strategies” Hersen (2004). Based on Hersen (2004), the neuropsychologist has to fulfill the following qualifications, after the doctoral degree in psychology:

- An internship, or its equivalent, in a clinically relevant area of professional psychology.
- The equivalent of two years of experience and specialized training.
- A license in his or her state or province to practice psychology and/or clinical neuropsychology independently, or is employed as a neuropsychologist by an exempt agency.

**Sequence of actions** This paragraph describes in detail the procedure of the Wada test and the cerebral angiogram, which has to be executed prior to of the Wada test. The cerebral angiogram depicts the blood flow within the brain to make sure that there are no obstacles to the ISAP. The neuroradiologist inserts a catheter (a long, narrow tube) into an artery, usually in the leg. The catheter is directed to the right or left internal carotid artery in the neck, which supplies the brain with blood. Once the catheter is in place, a dye is injected and can be seen on a special x-ray machine. This machine takes pictures of the dye as it flows through the blood vessels of the brain. Once the angiogram is done, the catheter will stay in place for the Wada test. The neuroradiologist starts the course of action with injection of sodium amobarbital into the either the left or right carotid artery.

“The left and right carotid arteries form together the common carotid artery and supplies the neck and head with blood. Each artery, left or right, supplies one side of the upper body, hence only either the right or left hemisphere of the brain” cf. Ashrafian (2007).

“The injection of sodium amobarbital has the pharmacological effect, that one hemi-

sphere falls asleep for a short time period. During the time the patient is in the hemiplegia phase, the neuropsychologist begins with the language test that includes several tasks e.g., naming the calendar days, following commands and naming of different objects shown on pictures. Especially for patients, who will undergo an operation on the temporal lobe the memory test is very important and therefore the neuropsychologist shows five to twelve memory objects during the anesthesia. Hence, the awake half of the brain has the job to remember, recognize and direct the language process of the brain. The language and memory test during the hemiplegia phase usually takes 10 to 15 minutes and when it is over the doctors ask the patient to retrieve the shown objects and pictures. They record the answers word for word and then start with the procedure for the other side. The delay between the two injections is normally 30 to 60 minutes and the second routine is the same as the first, except that now different pictures and objects are shown” cf. Weiner (2004).

## **2.3 Application field for functional brain mapping**

As mentioned earlier, many scientists have been working on exploring the human brain, but what are the application fields for this knowledge? Before we talk about application fields, we have to specify the term brain mapping more in detail. Brain mapping can be split into two main parts, conventional structural imaging and functional brain mapping. Based on Engel (1996), test for structural imaging are:

- X-ray films, computed tomography, and other radiographic studies
- MRI
- Magnetic resonance spectroscopy

On the other hand, functional MRI or electrocortical stimulation are considered functional brain mapping techniques. This work deals with both functional brain mapping and language lateralization, and these methods should not to be confused with techniques for identifying seizure foci.

Functional brain mapping and structure mapping methods jointly provide information about the relationship between the location of lesions and primary brain functions for operative planning. Functional brain mapping is performed to treat two specific diseases, brain tumor and epilepsy surgery. Therefore, lateralization and localization of brain function is normally a required preparation for epilepsy and brain tumor surgery, because these surgeries remove a part of the brain. The overall goal of any surgery is to avoid irreparable damage to the patient, so a brain surgery should not derogate any

functions of the brain. Thus, the medical team has to make sure that the removed part contains no fundamental brain function. If the doctors know the exact locations of brain functions and infected brain areas before a surgery, they can plan the position of the transections to ensure the best outcome. Therefore, brain function lateralization and localization provide very important information for the surgical team, and the following sections describe the surgeries in detail.

### **2.3.1 Epilepsy surgery**

This paragraph gives a short overview about epilepsy surgery. First, we define epileptic seizure and epilepsy.

“Epileptic seizure is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain” Fisher et al. (2005). “Epilepsy is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological, and social consequences of this condition. The definition of epilepsy requires the occurrence of at least one epileptic seizure and enduring alteration in the brain that increases the likelihood of future seizures” Fisher et al. (2005).

“Based on 1995 data, seizures and epilepsy are estimated to affect approximately 2.3 million people with 181,000 new cases per year in the United States” Epilepsy Foundation (2003), so epilepsy is one of the most common neurological disorders worldwide. “80% of the patients can be successfully treated with antiepileptic drugs, but for the other 20 % only epilepsy surgery can help. However, currently just a small portion of the potential surgical candidates are getting a surgery” cf. Engel (2003). Under general anesthesia, a multidisciplinary team of specialists usually operates the patient in an epileptic center and the operation itself takes a few hours. “Under normal circumstance, the patient can leave the hospital after a few days and the operation’s procedure normally includes the removal of the hippocampus’s anterior part, a small part of the temporal pole and the amygdala” cf. Engel (1996).

Modern epilepsy surgery methods aim to remove only the brain areas that contain seizure foci and to avoid damaging fundamental brain functions such as language, memory and motor functions. Therefore, the position of the seizure prone area as well as the position of the fundamental brain functions must be known. Different epilepsy excitability detection methods have been developed, based on Engel (1996):

- Noninvasive:
  - Routine interictal EEG
  - Video EEG, long-term monitoring EEG

- Ictal single-photon-emission computed tomography
- Interictal and ictal magnetoencephalography
- Functional MRI
- Invasive
  - Intraoperative electrocorticography
  - Stereotactic-depth-electrode, long-term recording
  - Subdural grid electrode, long-term recording

However, some evaluation procedures are performed during the surgery and some are part of the presurgical preparation.

**Presurgical preparation** The surgical team decides how much information and which evaluation methods are required. The normal presurgical preparation contains interictal and long term EEG monitoring, MRI imaging and positron emission tomography. These methods seek to find abnormalities and seized in the brain areas. On the other hand, memory and language lateralization are also typically explored before an epilepsy surgery. If the focus of the seizure is close to the language cortex, an accurate topographic localization of the language area is required to specify boundaries for surgical excision, because the doctor can make sure to avoid any damage in the language and memory regions.

In summary, if the methods for determining cerebral dominance, such as Wada test, show that the fundamental brain functions are located on the same hemisphere where seizure foci were found, functional brain mapping is then performed to localize brain functions near the seizure foci. In this mapping procedure, an awake craniotomy is executed as part of the presurgical preparation. In this procedure, doctors implant a Subdural Grid Electrode (see Figure 3.2 on page 31) above the seizure foci that was identified by noninvasive tests for epilepsy excitability. This Subdural Grid Electrode is used for two purposes. First, the data recorded from the Subdural Grid Electrode during an epileptic seizure can help precisely localize the seizure foci, because the invasive tests for epilepsy excitability have a higher resolution than a noninvasive test. Second, electrocortical stimulation, which localizes brain function, requires the Subdural Grid Electrode to stimulate the brain, and the Subdural Grid Electrode is implanted in an average for 15 days.



### 2.3.2 Brain tumor surgery

Besides epilepsy surgery, brain tumor surgery is the second application field for brain mapping. This paragraph provides general information, and then the subsection presurgical preparation explains the used methods. “Primary malignant brain tumors account for 2 percent of all cancers in U.S. adults. The American Cancer Society estimates that there are more than 18,000 new diagnoses of brain and nervous system cancers causing more than 12,000 deaths each year in the United States.” Sreenivasa R. Chandana (2008). The procedure of a brain tumor surgery is slightly different than an epileptic surgery, because the patient’s condition is stable over time. In other words, an epilepsy patient must have a seizure to detect the brain area prone to seizures, and it is not possible to predict or control the epileptic seizure. Thus, long-term monitoring is necessary to record and analyze the epileptic seizure.

**Presurgical preparation** for a brain tumor surgery does not include monitoring over time, but the goal of functional brain mapping is the same for epilepsy and brain tumor patients. Like epilepsy surgery, the medical team decides whether electrocortical stimulation is necessary to ensure the best outcome of the surgery, based on the result from the presurgical methods mentioned in table 2.2.

Modality	Uses
CT	Localizing the tumor and defining its dimensions, morphology
MRI	Localizing the tumor and surrounding structures with a high-resolution image, diagnosis of supra- and subtentorial tumors, diagnosis of extra- and intra-axial tumors, presurgical planning with three-dimensional imaging, stereotactic biopsy, radiotherapy
DTI	Establishing spatial relationships between tumor border and white matter, assessing the progression and regression of white matter tracts caused by tumor growth or resection
fMRI	Neurosurgical planning and neurologic risk assessment by localizing the cortical regions that control language, motor, and memory functions
MRA	Understanding tumor vascularity and identifying the anatomic relationship between the tumor and blood vessels
MRS	Obtaining biochemical and metabolic information about the tumor, determining tumor type and grade by assessing the cellular contents, differentiating tumor from radiation necrosis
PET	Metabolic assessment of tumor aggressiveness (grade), assessing the highly metabolic areas within the tumor, differentiating between tumor recurrence and radiation necrosis, functional localization of cortical regions, predicting patient survival and prognosis

CT = computed tomography; DTI = diffusion tensor imaging; fMRI = functional magnetic resonance imaging  
MRA = magnetic resonance angiography; MRI = magnetic resonance imaging; MRS = magnetic resonance spectroscopy  
PET = positron emission tomography

Table 2.2: Imaging Modalities for the Management of Primary Brain Tumors. “These imaging modalities can be helpful when performing the initial work-up and follow-up and in the evaluation and treatment of brain tumors” Sreenivasa R. Chandana (2008).

If yes, the doctors will first implant an electrical grid above the area where the brain tumor is diagnosed, and then electrical stimulation is performed to ensure that no primary brain functions like memory or language are situated in this area. The second part of the surgery is the removal of the affected section of the brain.

## 2.4 Summary of functional brain mapping

During preparation for epilepsy and brain tumor surgery, a surgical team may need to identify which brain regions are responsible for primary brain functions such as memory or language. Currently intracarotid amobarbital, or Wada test, has been the standard for language and memory lateralization. If the seizure focus is close to primary brain functions, then the physician implants a Subdural Grid Electrode for approximately 15 days, and executes both functional brain mapping and precise localization of the brain tumor or epileptic foci. Electroconvulsive stimulation is the established method for functional brain mapping. Afterwards, the tumor or epileptic foci and the Subdural Grid Electrode

are both removed in a second surgery. The need to replace the Wada test and electrical stimulation mapping with less invasive and more reliable techniques has long been recognized, both procedures are invasive and entail risks and discomfort.

Alternative brain imaging approaches include functional MRI and EEG. fMRI, which detects a blood oxygenation level dependent (BOLD) signal, can be used for lateralization and for functional brain mapping. fMRI has the advantages of excellent spatial resolution and safety, because it is a noninvasive procedure. However, fMRI systems have numerous practical problems. Due to the high purchase price, a fMRI device is only available in a few hospitals, and hospitals are not likely to purchase an fMRI just to support lateralization and localization efforts. fMRI systems require a very powerful magnetic field, which makes them impossible to use with persons who have pacemakers, neurostimulators, metal implants, or other special circumstances. Also, since fMRI analysis require patients to lie very still for extended times in a very noisy environment, they are unpleasant for most patients and impossible for some, such as persons with claustrophobia. Furthermore, lateralization and especially functional brain mapping are very scientific and complex tasks with fMRI, and therefore very few physicians are qualified. There also many concerns about the reliability of the fMRI for functional brain mapping, and hence most physicians verify the results from fMRI with the established methods anyway.

In conclusion, fMRI could theoretically be used for lateralization and functional brain mapping. However, in practice, there are too many disadvantages for it to be practical in the foreseeable future. Hence, fMRI is far away from becoming the new gold standard for language lateralization and functional brain mapping. Brain computer interface methods, on the other hand, suffer none of the disadvantages described here; instead, the main barrier to wider adoption is the absence of a well-known software platform that can make EEG-based mapping easy and effective.

### 3 Development results at Wadsworth Center

The last chapter explained the established methods for both functional brain mapping and language lateralization, which can be part of the epilepsy and brain tumor surgery. This chapter presents the two recently developed methods for functional brain mapping and language lateralization at the Wadsworth Center. The first innovative development result is known as **SIGFRIED**, which stands for “SIGnal modeling For Realtime Identification and Event Detection”. For the purpose of functional brain mapping, SIGFRIED speeds up the electrocortical stimulation procedure, which is the current gold standard. SIGFRIED could completely replace the electrocortical stimulation, but more research work is necessary. The second research outcome is called **EEG LI test** and, as the name indicates, this recently developed clinical diagnostic test involves language lateralization. Electroencephalography Lateralization Index test (EEG LI test) is an independent method and has many advantages compared to the Wada test, which is the current established method. A detailed description of the two recently developed

Used for	Gold standard	Emerging technology	Development result
Functional brain mapping	Electrocortical stimulation	Functional MRI	SIGFRIED
Language lateralization	Wada test	Functional MRI	EEG LI test

Table 3.1: Characteristics of the development results.

clinical diagnostic tests and an extensive comparison between these tests and their competitors is provided in the end of this chapter.

We will first present the a general description of the innovation procedure and than we discuss the innovation procedure at the Wadsworth center. The BCI group at the Wadsworth Center works on basic research, and then focuses on the resulting application field. Hence, we first describe the two development results, and the market demand is evaluated in chapter 4. We begin this section with the theoretical background of the innovation process.

### **3.1 General description of the innovation procedure**

The literature provides many variation of the definition of the term innovation and we use the definition by Schumpeter. "Innovation, that is the process of finding economic application for the inventions" of Economics, Schumpeter and Opie (1934). The following aspects of the term innovation are based on of Economics, Schumpeter and Opie (1934):

1. The introduction of a new good or a new quality of the good
2. The introduction of a new method of production
3. The opening of a new market
4. The conquest of a new source of supply
5. The carrying out of the new organization of an industry

This definition shows that there is a significant difference between the term invention and innovation. A invention is defined as the development result itself, the term innovation goes beyond that. It includes all the development stages of development result, beginning with an idea and ending at its introduction in the usage area. Generally a innovation can be understand as a change process undertaken by an organization for the first time.

The Organization for Economic Co-Operation and Development's document "The Measurement of Scientific and Technological Activities, Proposed Guidelines for Collecting and Interpreting Technological Innovation Data", also known as the Oslo Manual, defines four types of innovations, which are listed below.

"Product innovation is the introduction of a good or service that is new or significantly improved with respect to its characteristics or intended uses. This includes significant improvements in technical specifications, components and materials, incorporated software, user friendliness or other functional characteristics. Product innovations can utilize new knowledge or technologies, or can be based on new uses or combinations of existing knowledge or technologies" Bloch (2007).

"Process innovation is the implementation of a new or significantly improved production or delivery method. This includes significant changes in techniques, equipment and/or software. Process innovations can be intended to decrease unit costs of production or delivery, to increase quality, or to produce or deliver new or significantly improved products" Bloch (2007).

“Marketing innovation is the implementation of a new marketing method involving significant changes in product design or packaging, product placement, product promotion or pricing. Marketing innovations are aimed at better addressing customer needs, opening up new markets, or newly positioning a firm’s product on the market, with the objective of increasing the firm’s sales” Bloch (2007).

“Organizational innovation is the implementation of a new organizational method in the firm’s business practices, workplace organization or external relations. Organizational innovations can be intended to increase a firm’s performance by reducing administrative costs or transaction costs, improving workplace satisfaction, gaining access to non-tradable assets or reducing costs of supplies” Bloch (2007).

## **3.2 Innovation procedure at Wadsworth Center**

The Wadsworth group based their innovation procedure on the State-Gate process. Developed by Robert G. Cooper, State-Gate process is an operational model to develop a product consistently from idea generation to market entry. The State-Gate process divides the innovation process into pre-determined sequentially continuous stages, which consist of a subset of cross-functional and parallel activities. accordingly to the idea of process orientation, employees of different functional divisions perform the wide range of technical, market and value-related activities.

Each new section is entered through a gate that has the goal to evaluate and control the step-by-step realized results of innovation process. After each gate, the innovator team decides whether they move on with the process or to refuse the idea. The structure of all gates are similar and consist of result’s allowance, appraisal factors and approved decisions. For the next gate, the innovation team leader always appoints the result’s allowance at the previous gate and the leader communicates them through the whole team. The appraisal factors consist of necessary and desirable criteria, which can be fulfilled in varying degrees and forms a basis for the classification of priorities between different development projects. Approved decisions are the results of each gate, which results in three outcomes: continuation, adjusting, or revising the considered development projects. The decision also includes a plan of action, that organizes resources such as personnel, budget and time limit for the next stage.

The structure of stages and gates is characteristic for the State-Gate process and has led to its naming. The Figure 3.1 on page 28 is an overview of the idealized Stage Gate process developed by Robert G. Cooper, that is adapted and adjusted to each situation depending on the individual company.

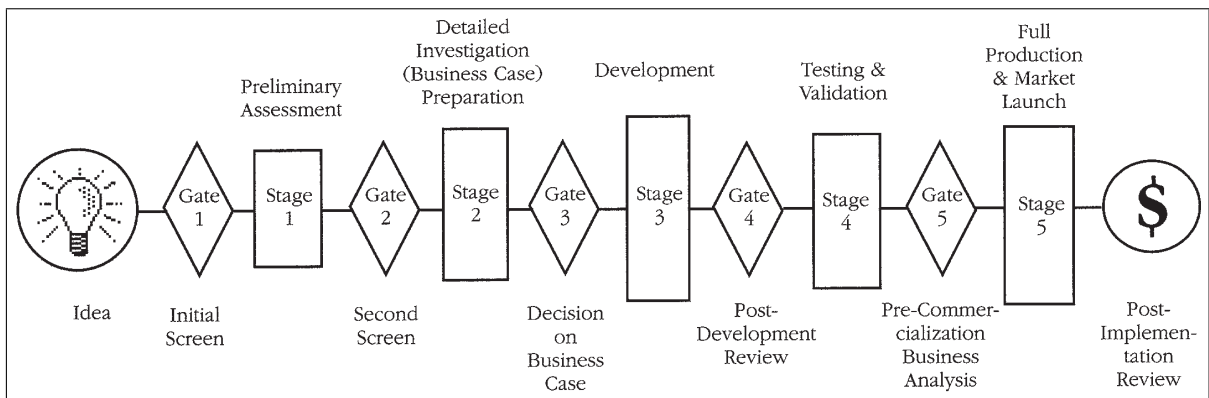


Figure 3.1: Stage gate process. “Stage gate process divides the innovation procedure in gates and stages and at each gate, the responsible project members decide whether continuation, adjusting, or revising the considered development project” Cooper (1990).

The basic concept by Cooper of product innovation process is divided into five stages, “Preliminary Assessment”, “Detailed Investigation Preparation”, “Development”, “Testing & Validation” and “Full Production and Market Launch” as referred to Cooper. Each stage is designed so that both all required information are collected and conditions are met, which are necessary in order to be able to pass the following gate. The first gate in front is the phase development that is not explicitly included in the basic concept as a separate stage. However, Cooper points out that many companies treat this phase as a formal stage, because of its high importance for them.

**Gate 1: Initial Screen** The first gate assesses the rough idea and assigns both required and desirable criteria to the project. Financial or monetary measurable criteria are not given in this early stage, because in practice a correct estimation is too complex in the most cases.

**Stage 1: Preliminary Assessment** The aim of this stage is to determine the technical and market advantages of the development project, which will be a final product at a later date, in the form of a first overview.

**Gate 2: Second Screen** The second gate assesses much more concrete the idea on the basis of the first stage’s obtained information and the appraisal factors established at first gate. In addition, financial aspects are considered in the idea evaluation.

**Stage 2: Detailed Investigation Preparation** Subject of the second stage is a detailed analysis of the development project that includes a market-based and technical research. The goal is to create an entrepreneurial framework for the project and a

definition of the final product. The development project is justified in terms of market and technology perspective, which is normally reached with an income statement and a detailed financial analysis of the project.

**Gate 3: Decision on Business Case** The third gate is the last point before the physical development starts of the future product. According to Cooper, it is the last point at which the development project can be canceled without the occurrence of massive costs, but it is worth to notice that also costs incurred until this gate. Generally, this Gate deals with the review of the second stage's results and to assess whether the development projects should be pursued. The assessment is done on the basis of required and desirable criteria established at the second gate.

**Stage 3: Development** In the third stage is the implementation of the development plan and the physical development of the product. The focus is on the technical work, however, other activities such as customer surveys and economic analysis take place parallel, and the results can lead to iterative loops in the development process.

**Gate 4: Post-Development Review** Subject of the fourth gate is the update control of the unchanged technical and economic attractiveness of the product. The results of the third stages are compared with the goals, which were ascertained at the third gate. The primary gate four output comprises of an inspection and test plans for the stage four and a review of the marketing plans as well as checking of the production schedule, which would enter into force in case of product launching.

**Stage 4: Testing & Validation** In this stage the product is rigorously tested and validated. In addition to testing, the actual products include the testing and validation of the production process, the acceptance by the customer as well as a review of the already made cost-analysis based on accurate data on revenues, costs and payment information.

**Gate 5: Pre-commercialization Business Analysis** This gate is focused on the results of the preceding test and validation section as well as to the adequacy of the production and marketing plans.

**Stage 5 :Full Production & Market Launch** In this final section, the production and marketing strategy are realized into practice. After a defined period the formed innovation project team will be dissolved and a product management team takes over.



**Post Implementation review** Before dissolution of the project team, it seems advisable to assess the project and its expiry review, to be able to learn from the strengths and weaknesses of project implementation were made for future development projects. As shown, the Stage Gate process provides a concept to structure the development plan. Furthermore the Stage Gate process improves the predictability of the development result procedure and it supports a consistent implementation from idea to market. The results of previous sections affect the objectives of the follow-up phase, hence the overall context of the development project is emphasized explicitly. In summary, the Wadsworth group follows the structure of the State Gate process and it is worth noticing that some development projects require minor adjustments of this structure.

### **3.3 Development result SIGFRIED**

The method “SIGnal modeling For Realtime Identification and Event Detection” (SIGFRIED) was invented by the BCI group at the Wadsworth Center in cooperation with the Albany Medical College and SIGFRIED is a novel technique for functional brain mapping. In 2009, the first paper was published in the Journal of Epilepsy & Behavior with the title “*A practical procedure for real-time functional mapping of eloquent cortex using electrocorticographic signals in humans*” and since then, functional brain mapping was performed approximately 60 times with SIGFRIED. It is important to reiterate that SIGFRIED was reviewed by an Institutional Review Board (IRB) (see Section 5.1) and the (IRB) decided that SIGFRIED can only be used for research purposes. For communalization, SIGFRIED must pass the approval process of the Food and Drug Administration (see Section 5.2) and this work describes the regulatory environment in chapter 5. This section explains the operating mode and component of SIGFRIED. However, SIGFRIED records data from subdural grid, which is normally implanted in brain tumor or epileptic patient for the intention of electrocortical stimulation. The implantation of the Subdural Grid Electrode is called craniotomy, which indicates a surgical operation where a bone flap is temporary removed to access the skull (see Figure 3.2). Both SIGFRIED and electrocortical stimulation execute functional brain mapping, but the essential technology difference between them is that SIGFRIED records the electrical brain waves and does not stimulate the brain at all. In other word, both methods require the same implanted grid and have the same intend use, which is functional brain mapping, but SIGFRIED never actively stimulates the brain.

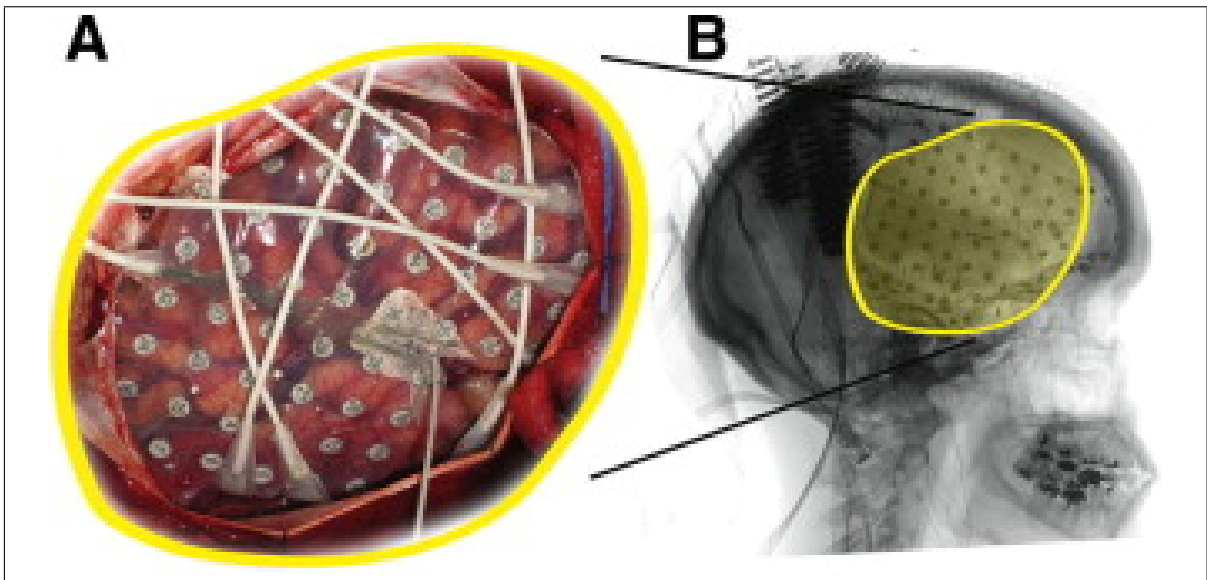


Figure 3.2: Implanted subdural grid. “Example of an implanted subdural grid in a patient. (A) Subdural grid placed over frontoparietal areas. (B) Lateral radiograph indicating the position of the grid” Brunner et al. (2009).

**Mode of operation** “The subject is presented with visual cues shown on a computer monitor while electrocorticographic signals are recorded. Both the patient screen and the data acquisition device are interfaced with a laptop computer running BCI2000. BCI2000 acquires signals from the device, submits these signals in real time to the SIGFRIED method, and presents the results visually in a topographical display to the investigator” Brunner et al. (2009). Dr. Schalk and his team improves SIGFRIED con-

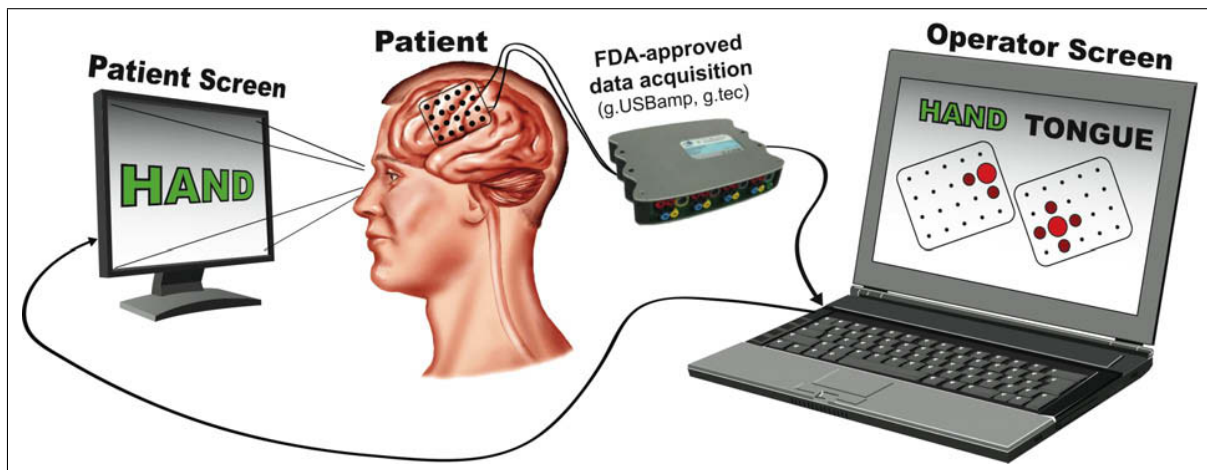


Figure 3.3: “Equipment setup of SIGFRIED” Brunner et al. (2009).

tinuously and the last version includes a three dimensional topographical map of the detected brain functions.

### 3.3.1 Components of SIGFRIED

The Table 3.2 on page 32 contains the required hardware to run SIGFRIED, and each hardware component can be used without any modification. This point is very important for the further pre-commercial development, because the hardware components Subdural Grid Electrode and g.USBamp are already FDA approved for that intended use.

Item	Company name	Prize [USD]
Subdural Grid Electrode	Ad-Tech Medical Instrument Corporation	1000
g.USBamp	g.tec medical engineering GmbH	20,000
Inspiron 1545	Dell Inc.	499
Laser printer 1110	Dell Inc.	69
Cables	Miscellaneous	70
Cart	Miscellaneous	400
Total hardware costs of SIGFRIED		<b>22,138</b>

Table 3.2: Compilation of all hardware components for a SIGFRIED.

The software that is the innovative part of the SIGFRIED system runs on the BCI2000 platform and is programmed in Matlab™. To execute the SIGFRIED, the Visual Studio 2010 Professional software package is required, and SIGFRIED's results are depicted as a PDF document. The required software for a SIGFRIED system is shown in Table 3.3 on page 32.

In conclusion, SIGFRIED software coupled with BCI2000 can lead to a system for functional brain mapping and Figure 3.3 on page 31 displays the complete system without the cart.

Item	Company name	Prize [USD]
BCI2000	Wadsworth Center	NA
SIGFRIED software	Wadsworth Center	NA
Window 7 Home Premium	Microsoft	0*
Visual Studio 2010 Professional	Microsoft	1,200
Adobe Reader 9.4	Adobe Systems Inc.	0
Total software costs of SIGFRIED		<b>1,200</b>

Table 3.3: Compilation of all software components for SIGFRIED. \* The operating system (Windows 7 Home Premium) comes with the laptop (an Inspiron 1545) and is included in the price of the laptop.

Since SIGFRIED can only be used for research purposes, the Albany Medical Center performs SIGFRIED in addition to electrocortical stimulation. The results of

SIGFRIED can thus be verified and evaluated with the outcome of electrocortical stimulation, which is the current gold standard in functional brain mapping.

### 3.3.2 Technical comparison against the established method

SIGFRIED’s biggest advantages are the short duration time of two hours and patient safety, because our system relies on passive recording of the brain waves without actively stimulating the brain. Currently SIGFRIED is performed upfront electrocortical stimulation, and based on the results of SIGFRIED, the order of electrocortical stimulation’s procedure is adjusted. In particular, the Neurologist starts stimulating at the areas where SIGFRIED already detected relevant brain function, and hence the electrocortical stimulation procedure is optimized with SIGFRIED’s results. SIGFRIED has many advantages over electrocortical stimulation, which are listed in 3.4.

	Electrocortical stimulation	SIGFRIED
Time consuming	Yes	No
Risk of seizure induction	Yes	No
Difficulty in observing inhibit response	Yes	No
Necessity for antiepileptic drugs	Yes	No
Variable property of stimulation current	Yes	No
Procedural variability	Yes	No
Nonphysiological model	Yes	No
Patient compliance necessary	Yes	Currently yes
Proven by clinical studies	Yes	Not yet

Table 3.4: Comparison of electrocortical stimulation and SIGFRIED]. “Comparison of the properties of electrocortical stimulation and SIGFRIED” Brunner et al. (2009).

In summary, SIGFRIED has several advantages compared to electrocortical stimulation.

### 3.3.3 Economical comparison against the established method

Beside clinical effectiveness, cost-effectiveness plays a major role in the innovation process of a medical device. Functional brain mapping has two applications field brain tumor and epilepsy surgery. First we show the cost-effectiveness of these surgeries, and then we discuss the cost-saving potential of SIGFRIED compared to the current gold standard electrocortical stimulation.

**Epilepsy surgery** According to the paper “*Cost-Effectiveness of Anterotemporal Lobectomy in Medically Intractable Complex Partial Epilepsy*”, functional brain mapping costs \$29,286 on average per patient. On average means that for only 45% of all Anterotemporal lobectomy (ATL) cases, functional brain mapping is required and \$29,286

reflects discounted costs per patient. Furthermore, this paper evaluates the cost-effectiveness of ATL compared to with standard medical management in medically-intractable epilepsy.

“Anterotemporal lobectomy (ATL) is an effective treatment for selected patients with medically intractable complex partial temporal lobe seizures. The per patient cost of presurgical evaluation and surgery has been estimated at \$25,000–\$100,000 depending on the complexity of the case. ATL is the most frequently and successfully performed epilepsy surgery. Base case and sensitivity analysis suggest that under the most plausible clinical circumstances, evaluation for ATL is likely to be both more costly and more effective than standard medical management over the lifetime of the patient, from the perspective of the provider. Only under the most optimistic assumptions of the model was evaluation associated with long-term cost savings” cf. Langfitt (1997). The Chart 3.4 shows that “inpatient depth monitoring, which equals functional brain mapping, costs \$55,364 per hospitalization, thus this is by far the most expensive part of the epilepsy treatment costs” cf. Begley et al. (2000).

Cost items	Cost measures	Unit cost	Source of cost
<b>Physician and hospital services</b>			
Emergency room visits	Routine cost per visit	233	Cost-to-charge <sup>a</sup>
Hospital admissions	Routine cost per hosp	2,385	Cost-to-charge
Inpatient physician visits	Cost per visit	65	MFS <sup>b</sup>
Outpatient physician visits	Cost per initial visit	63	MFS
	Cost per follow-up visit	48	MFS
<b>Diagnostic procedures</b>			
EEG	Cost per procedure	117	MFS
CT scan	Cost per procedure	249	MFS
MRI	Cost per procedure	643	MFS
Other radiologic procedure	Cost per procedure	54	MFS
Lumbar puncture	Cost per procedure	66	MFS
Neuropsychological testing	Cost per procedure	78	MFS
<b>Laboratory tests</b>			
AED blood levels	Cost per procedure	18	MFS <sup>c</sup>
Other diagnostic lab tests	Cost per procedure	10	MFS
<b>Other</b>			
Emergency transportation	Cost per trip	181	Tx Medicaid <sup>d</sup>
Other services and procedures	Cost per procedure	56	MFS
<b>AED treatment</b>			
AEDs	Cost per year		Red Book <sup>f</sup>
<b>Surgery</b>			
Initial outpatient evaluation	Cost for vis & proc	2,134	King et al. <sup>g</sup>
Inpatient surface monitoring	Cost per hospitalization	12,268	King et al.
Inpatient depth monitoring	Cost per hospitalization	55,364	King et al.
Surgery	Cost per hospitalization	17,652	King et al.
<sup>a</sup> Hospital-based charges were translated into cost by applying the cost-to-charge ratios from each hospital's Medicare cost report. <sup>b</sup> Medicare Resource-Based Physician Fees for professional services (8). <sup>c</sup> Based on average Medicare payments adjusted to 1995 dollars (9). <sup>d</sup> Texas Medicaid Payment Rate (personal communication, Texas Medicaid officials). <sup>e</sup> Varies with drug type and dosage. <sup>f</sup> 1995 wholesale drug prices from the Drug Topics Red Book (10). <sup>g</sup> Based on published data reported by King et al. (11), and updated to 1995.			

Chart 3.4: Medical care items captured in the treatment of epilepsy. "As indicated in the last column of the table, nationally representative unit costs were used whenever possible (i.e., the national Medicare payment rate for physician visits, procedures, and laboratory tests, and the national wholesale drug price for AEDs). Inpatient depth monitoring is by far the most expensive part of epilepsy treatment" cf. Begley et al. (2000).

The paper "A cost-effectiveness analysis of anterior temporal lobectomy for intractable temporal lobe epilepsy" determines the inpatient depth monitoring costs precisely for ATL patients. The average total protocol cost for evaluation and treatment per ATL patient is \$38,500. This number can be spilt into 4 parts. Inpatient depth

Task	Cost [USD]
Initial outpatient evaluation	2,120
Inpatient surface video monitoring	11,106
Inpatient depth electrode video-EEG monitoring	49,296
Admission for Anterior temporal lobectomy (ATL) with mean length of stay 6 days	16,079

Table 3.5: ATL average cost per patient. “The table lists the average cost per anterior temporal lobectomy for intractable temporal lobe epilepsy patient. As we have noted, not all patients undergo each stage of the evaluation and treatment protocol, so the average total procedure cost per patient is \$38,500” King et al. (1997).

electrode video-EEG monitoring was necessary in 29% of all patients, which explains why the average total cost is lower than the sum of the enumerated costs. Part of the Inpatient depth electrode video-EEG monitoring procedure is functional brain mapping, and SIGFRIED can be used for this purpose. The Table 3.6 on page 36 breaks down the costs for inpatient depth electrode video-EEG monitoring.

Item	CPT	Cost [USD]
Neurology initial	9954	123
Neurology daily	99262	587
Neurology discharge	99238	55
Video-EEG-professional (\$184.46/24hr)	95951–26	2,764
EEG - mapping/stimulation (1 st hr)	9561–26	155
Wada test - neurology professional	95958–26	174
Wada test - radiology professional	75671	300
Neurosurgeon - professional (stereotactic depth electrodes)	61760	1,532
Neurosurgeon - professional (subdural strip electrodes)	61531	688
Anesthesiologist	N/A	712
Arterial line - professional	36620	68
MR imaging (90% of patients @\$84.92)	70450–26	76
CT,no contrast - professional (10% of patients @\$48.86)	70250–26	5
Skull x-ray films	70250–26	14
Hospital reimbursement (median cost)	NA	42,043
<b>Total costs of inpatient depth electrode video-EEG monitoring</b>		<b>49,296</b>

Table 3.6: Admission for depth electrode video-EEG monitoring. “Hospital reimbursement causes for most of the costs. King et al. reported a mean length of stay 15 days and SIGFRIED could significant lower the mean length of stay and the EEG - mapping/stimulation time” King et al. (1997).

The last three papers proved that most of the cost in epilepsy surgeries result from functional brain mapping, in particular the hospital reimbursement (median cost) for the 15 of stay mainly due the high costs.

In conclusion, SIGFRIED’s shorter duration time will result in large cost savings com-

pared to electrocortical stimulation. In general, functional brain mapping has a high cost saving potential, because it substantially reduces the largest epilepsy treatment cost. There are no adequate cost-effectiveness studies available for brain tumor surgery. However, since epilepsy and brain tumor surgeries involve similar procedures, SIGFRIED could reduce costs of brain tumor surgery.

### **3.4 Development result EEG LI test**

The BCI group at the Wadsworth Center developed the novel technology “EEG LI test” in 2009. As the name indicates, this non-invasive technology performs language lateralization based on electrical activity recorded outside the scalp. At this stage the BCI group at the Wadsworth Center conducted one study in accordance with the guidelines for the use of human subjects and approved by the Review Board of Albany Medical College. The results of this study will be published in the near future.

**Mode of operation** In this study, the BCI group at the Wadsworth Center used 64-channel EEG and the BCI 2000 platform (see Section 1.4) to evaluate hemispheric language dominance during four language tasks in 22 right- and left-handed healthy volunteers and one left-handed epilepsy patient. The language tasks included word repetition, oddball recognition, complex listening, and animation description and data was recorded from the scalp’s surface overlying Wernicke’s and Broca. The study was carried out in two experimental sessions lasting approximately 1 h each. The sessions were conducted in a quiet room with dimmed lights. BCI2000 was also used to analyze the resulting data, and a significant correlation was found between the EEG signals and language dominance. Based on this correlation, a new parameter is defined, Lateral Index (LI), to characterize the lateralization of language. If the language is dominant over right hemisphere, the LI has positive value, and the LI is negative if language is dominant over the left hemisphere.

In summary, this study demonstrated that 64-channel EEG coupled to the BCI2000 platform could be used to assess language lateralization in humans.



### 3.4.1 Components of EEG LI test

The Table 3.7 lists the required software components for a EEG LI test system.

Item	Company name	Prize [USD]
BCI2000	Wadsworth Center	NA
EEG LI test software	Wadsworth Center	NA
Window 7 Home Premium	Microsoft	0*
Visual Studio 2010 Professional	Microsoft	1,200
Adobe Reader 9.4	Adobe Systems Inc.	0
Total software costs of EEG LI test		<b>1,200</b>

Table 3.7: Compilation of all software components for a EEG LI test system. \* The operating system, Windows 7 Home Premium, comes with the laptop, Inspiron 1545 and it is included in the prize of the laptop.

The core of the EEG LI test system is the novel signal processing software algorithm, which detects and calculates the Lateral Index (LI) and runs on the BCI2000 platform. The novel signal processing software algorithm is written in the computer language Matlab™, and Visual Studio 2010 Professional is required to run the application. The signal processing software algorithm's result, Lateral Index, is reported as a pdf document. Both the BCI2000 platform and the EEG LI test's processing software algorithms were developed by the BCI group at the Wadsworth Center, but currently these software tools are only approved for research purposes. For commercial use, both software systems need an Food and Drug Administration approval, which necessitates further development and expenses. At this point, the effort for the approval process is unclear, and thus an realistic estimation of the expenses is too complex. All required hardware components are off the self products and each element is used for its intended purpose without any modification.

Item	Company name	Prize [USD]
g.EEGcap	g.tec medical engineering GmbH	300
g.USBamp	g.tec medical engineering GmbH	20,000
Inspiron 1545	Dell Inc.	499
Laser printer 1110	Dell Inc.	69
Cables	Miscellaneous	70
Cart	Miscellaneous	400
Total hardware costs of EEG LI test		<b>21,338</b>

Table 3.8: Compilation of hardware components for a EEG LI test system.

The software and hardware components jointly form the EEG LI test system.

### 3.4.2 Comparison against the established methods

Compared to the current gold standard, the Wada test, EEG LI test system is not yet able to determine memory lateralization, but EEG-based memory lateralization is conceivable in the future. On the other hand, EEG LI test provides many advantages compared to the Wada test, which has numerous problems.

“**The Wada test** is an invasive test that involves an arteriogram and the risks associated with an arteriogram. In one study, the risk of carotid artery dissection was 0.7% (Loddenkemper, Morris and Perl (2002)). Other potential complications of the Wada test include cerebral infarction, transient femoral neuropathy, and arterial spasm with potential transient deficits. The invasive nature of the Wada test makes it unsuitable to study language dominance in normal volunteers or in any group where the results are not essential for treatment” cf. Abou-Khalil (2007b). The Table 3.9 on page 39 summarizes the differences between the Wada test and EEG LI test. In conclusion, EEG LI

	Wada test	EEG LI test
Invasive procedure	Yes	No
Risk of carotid artery dissection	Yes (0.7%)	No
Risk of complications	Yes	No
Time consuming	Yes	No
Intracarotid injection of an anesthetic	Yes	No
Angiography suite required	Yes	No
Proven by clinical studies	Yes	Not yet
Requires medical expert	Yes	No
Estimated cost per procedure	High	Low

Table 3.9: Comparison of the properties of Wada test mapping and EEG LI test.

test has many advantage compared to Wada test.

**Functional Magnetic Resonance Imaging (fMRI)** is an emerging technology for the assessment of cerebral language dominance, and this paragraph points out the significant differences between EEG and fMRI-based assessment of language lateralization supported by the article *“Methods for determination of language dominance: the Wada test and proposed noninvasive alternatives”*.

“It has an excellent spatial resolution and it can provide both localization and lateralization. fMRI can be repeated many times without risk to the patient, because it is a non-invasive technology. However, fMRI is not possible in patients who are claustrophobic, excessively obese, and who cannot lie still. The need to be still and keep the head in the same position limits the monitoring of performance. Most of the fMRI tests

are covert, and it is difficult to be sure that the patient is performing the tasks required. fMRI is not possible in individuals who have metal in their head or those who have a pacemaker. “The presence of vascular malformations with high flow or large structural lesions can result in false lateralization and localization of language functions” Lehericy et al. (2002). In such cases, MEG can prove to be superior because it directly measures neurophysiologic activation rather than the hemodynamic response to cerebral activation. MEG also has a very high temporal resolution, making it possible to exclude from consideration activation of primary sensory cortex, which occurs within 200 ms from the stimulus. In addition, MEG can be complementary to fMRI in some instances, such that a combination of the two tests has perfect concordance with the Wada test Kamada et al. (2007). However, MEG is not widely available and it is expensive, making it an option only in major medical centers” cf. Abou-Khalil (2007a).

### **3.4.3 Cost-effectiveness analysis**

The primary goal for a development result is to be more cost-effective than the established devices on the market and the paper “*Functional MR Imaging versus Wada test for Evaluation of Language Lateralization: Cost Analysis*” evaluated the cost-effectiveness of the Wada test versus fMRI, published in the year 2004. This paragraph highlights the findings of this paper and we compare them with EEG LI test system costs.

The result of the paper is that “The total direct costs of the Wada test

**\$1,130.01 ± \$138.40**

and of functional MR imaging

**\$301.82 ± \$10.65**

were significantly different ( $P < .001$ ). The cost of the Wada test was 3.7 times higher than that of functional MR imaging” Medina et al. (2004).

Comparison of Direct Fixed and Variable Costs for Wada Test versus Functional MR Imaging			
Cost Category	Wada Test*	Functional MR Imaging †	Mean Relative Cost ‡
Fixed cost (\$)	299.19 ± 86.01	124.83 ± 2.41	2.40
Variable costs (\$)	830.82 ± 105.83	176.99 ± 9.40	4.70
Total physician labor	440.83 ± 95.20	147.63 ± 4.96	2.99
Radiologists	324.02 ± 100.34	147.63 ± 4.96	2.19
Neurologists	116.81 ± 8.00	NA	...
Total nonphysician labor §	185.47 ± 20.32	28.11 ± 6.70	6.60
Radiology nonphysicians	138.14 ± 23.14	28.11 ± 6.70	4.91
Neurology nonphysicians	47.33 ± 5.00	NA	...
Total variable supplies	204.52 ± 6.81	1.25	163.62
Variable contrast material	63.43 ± 28.46	0	...
Total direct cost (\$)	1,130.01 ± 138.40	301.82 ± 10.65	3.74

Note. —Data are means ± SDs unless otherwise indicated. NA = not applicable.  
\* Wada test was performed in 18 patients with a mean age ± SD of 19.2 years ± 5.4.  
† Functional MR imaging was performed in 21 patients with a mean age of 15.5 years ± 8.9.  
‡ Ratio of the cost of Wada test to the cost of evaluation with functional MR imaging.  
§ Costs of labor by technologists and nurses.

Chart 3.5: Total direct cost of Wada test and fMRI. “Fixed direct costs included the costs of equipment purchase, depreciation, maintenance, and service. Variable direct costs included the costs of labor and materials directly attributable to the performance of the procedures. Because indirect costs are incurred regardless of the procedure performed, they were excluded from the statistical analysis” Medina et al. (2004).

The analysis is based on the unit costs displayed in Chart 3.6, and a closer look at the numbers shows that the fixed costs, which include equipment purchase, depreciation, maintenance, and service, are slightly more expensive for the Wada test than for the fMRI, but the labor cost for the Wada test procedure are much greater than for the fMRI.

Unit Cost Estimates for Base Case	
Resource	Cost*
Purchase of 1.5-T MR imager	1,500,000
Purchase of angiography suite	1,800,000
Purchase of EEG unit	20,000
Purchase off unctional MR imaging audiovisual hardware and processing software	27,680
Yearly service and maintenance contract for 1.5-T MR imager	95,000
Yearly service and maintenance contract for angiography suite	120,000
Yearly service and maintenance contract for EEG unit	4,000
Yearly service and maintenance contract for functional MR imaging hardware and software	5,500
Weekly use of 1.5-T MR imager (h)	70
Weekly use of angiography suite (h)	40
Cost of images per functional MR case	3–7
Cost of images per angiographic case	16–24
Hourly salary per radiologist	120
Hourly salary per radiology technologist	25
Hourly salary per functional MR imaging scientist	50
Hourly salary per neurologist	85
Hourly salary per EEG technologist	16
Hourly salary per registered nurse	26
Angiography tray	50.64
Introducer set	20.75
Catheters (one to two)	20.25–40.50
Guidewires (one to two)	18.00–51.55
loversol (100 mL)	34.75
lohexol (100 mL)	89.94

\* Cost in U.S. dollars unless otherwise specified.

Chart 3.6: The unit cost of fMRI and Wada test. “The fMRI procedure generates direct fixed for equipment purchase, depreciation, maintenance, and service of the fMRI imager and variable costs that are mainly labor costs. The EEG related and variable supply costs that are Angiography tray, Introducer set, Catheters, Guidewires, loversol and lohexol count to the Wada test procedure” Medina et al. (2004).

We next compare the costs of EEG LI test with the costs of fMRI for language lateralization. At this early stage of the innovation process, the unit cost of EEG LI test are rough estimations based on assumptions. Hence, the goal of this comparison is to provide a first indication of EEG LI test’s cost-effectiveness. The following assumptions are made:

**Device related costs assumptions** The total hardware costs are \$21,338 and we assume a retail price of \$30,000. A prise estimation of the EEG LI test software prize is difficult, because the volume of the certification is currently unclear, but through several interviews with software engineers, there is evidence that \$30,000 is a realistic price for EEG LI test software. The next assumption is that the yearly service and

maintenance contract hardware and software expenses should be the same for fMRI and EEG LI test. The Table 3.10 summaries the device related costs between EEG and fMRI-based assessment of language lateralization.

Resource	fMRI [USD]	EEG LI test [USD]
Purchase of device	1,500,000	30,000
Purchase of software	27,680	30,000
Yearly service and maintenance contract for device	95,000	4,000
Yearly service and maintenance contract hardware and software	5,500	5,500
Sum of device related costs for a hospital	1,628,180	69,500

Table 3.10: Comparison of device related cost, which occur for a hospital.

**Variable labor costs assumptions** “The mean duration of patient examinations with functional MR imaging was 41 minutes +/- 8 minutes” Medina et al. (2004). Currently, the duration of EEG LI test was approximately 2 hours, but our team is confident that we can reduce the duration. We expect that our revised EEG LI test procedure will be as fast as fMRI, and also the number of physicians involved in both procedure should be equivalent. Hence there should not be a significant difference between the variable labor costs of fMRI or EEG LI test.

### 3.5 Summary of development results

The BCI2000 Group at Wadsworth Center developed two novel clinical diagnostic tests, SIGFRIED and EEG LI test. Both tests have significant advantages in terms of patient safety, time- and cost-effectiveness compared to the current established methods. Both development results are only accredited for research purposes and for commercial distribution additional certification is required. Currently, the complexity of the additional certification is unknown, thus an estimation of the certification’s effort and expenses is not possible at the current stage. But obviously it makes only sense to obtain and pay for the additional certification, if there is an adequate market demand for the innovative tests. The chapter 4 evaluates the clinical diagnostic tests’ market demand and the chapter 5 shows the effort and time for the certification. In addition, the chapter 6 and 7 complete the feasibility study of the two clinical diagnostic tests.

## 4 Evaluation of development results' market

The last chapter described the two recently developed clinical diagnostic tests at the Wadsworth center, and a critical step in the innovation process is the evaluation of the market demand. The two development results are in an early stage of the innovation process, and the BCI group at the Wadsworth Center has never executed any investigation to determine the development outcome's market demand. Thus, this chapter focuses on the validation of existing market studies to find a first indication of the market demand, which is sufficient for now. The market for a medical innovation has a special characteristic: the end user (the patient) does not usually pay directly for the treatment. The patient's insurance reimburses the hospital or private physician. Hence, the hospital or private physicians purchase the device from the medical device companies, and the patient's insurance companies are the hospital or private physician's customers. In order to assess coherent market demand, we evaluate two issues for each novel test. First, we address the number of hospitals and private physicians with the interest and qualifications to use the development result. Second, we explore the number of patients that benefit from the clinical diagnostic test. The subsequent chapter discusses the medical device's regulatory environment and is followed by the chapter on reimbursement, which explains the reimbursement process of the insurance companies and the reimbursement codes e.g., CPT codes, which dictate the amount that can be reimbursed.

**Target customer** To evaluate the market demand, the innovation's customer must be defined. The end customers of a medical device are the patients, who profit from the medical device development result. The next paragraph summarizes a relevant interview with a practicing neurologist, Anthony Ritaccio MD, who is director of the epilepsy and human functional brain mapping program at the Albany Medical Center. Dr. Ritaccio assumes that an EEG LI test device can be operated by every psychologist after the psychometric tests. Every epileptic and brain tumor patient undergoes at

least one EEG monitoring session during the therapy. In his opinion, since the phases of introducing and accepting new medicare methods like EEG LI test take a long time, only the hospitals that specialize in epilepsy and brain tumor patients will be interested in purchasing this new device in the beginning. After the development result is an established technique in some hospitals, private neurologists will become viable target customers. According to Dr. Ritaccio, the target customers of SIGFRIED are the hospitals that currently provide electrocortical stimulation, and obviously all patients who are subject to electrocortical stimulation.

**Market demand** The literature provides many different ways to measure the market demand, and the terminology for each market demand varies from book to book. The next paragraph presents the terminology of market demands from the book “Marketing Management” by Philip Kotler and Kevin Lane Keller, which is a very well established source.

“Companies can prepare as many as 90 different types of demand estimates (see Figure 4.1 on page 45. Demand can be measured for six different product levels, five

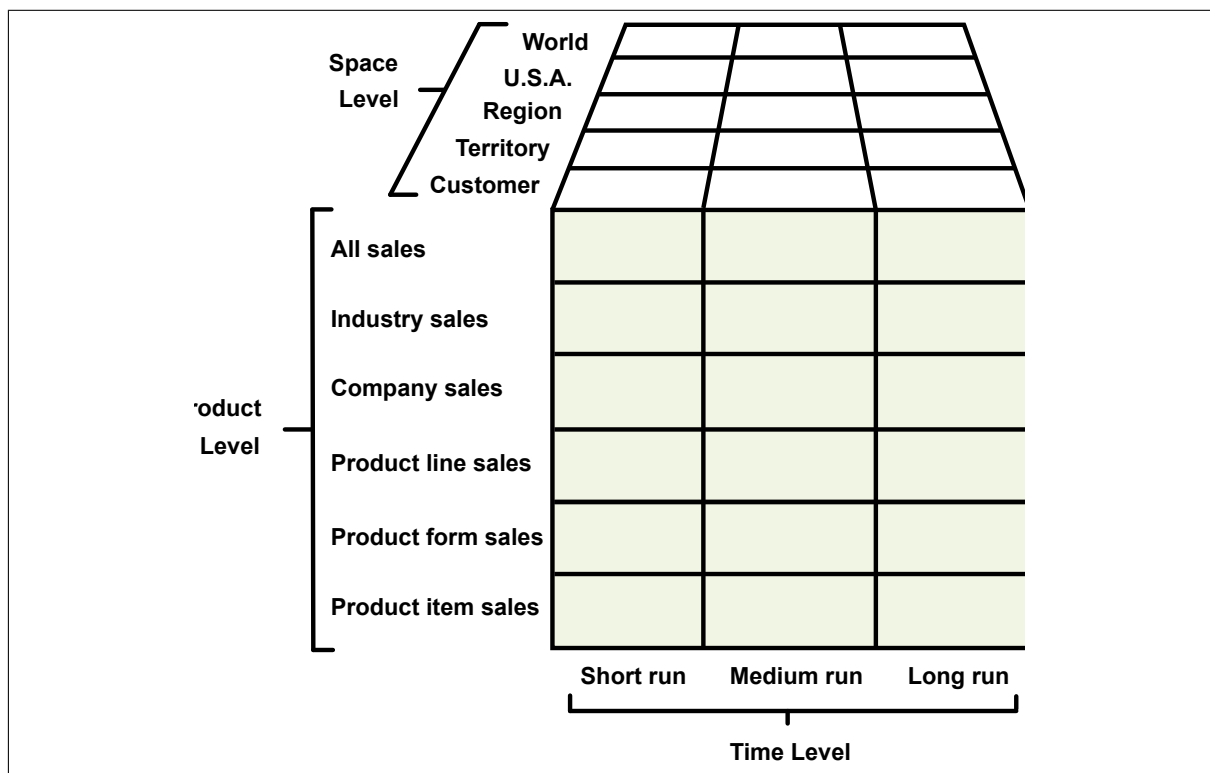


Figure 4.1: “Types of market demand” Philip Kotler (2006).

different space levels, and three different time levels. Each demand measure serves a specific purpose. A company might forecast short-run demand for a particular product for the purpose of ordering raw materials, planning production, and borrowing cash. It might forecast regional demand for its major product line to decide whether to set



up regional distribution. Forecasts also depend on which type of market is being considered. The size of a market hinges on the number of buyers who might exist for a particular market offer. But there are many productive ways to break down the market:" Philip Kotler (2006)

"The potential market is the set of consumers who profess a sufficient level of interest in a market offer. However, consumer interest is not enough to define a market. Potential consumers must have enough income and must have access to the product offer. The available market is the set of consumers who have interest, income, and access to a particular offer. For some market offers, the company or government may restrict sales to certain groups. For example, a particular state might ban motorcycle sales to anyone under 21 years of age. The eligible adults constitute the qualified available market—the set of consumers who have interest, income, access, and qualifications for the particular market offer.

The target market is the part of the qualified available market the company decides to pursue. The company might decide to concentrate its marketing and distribution effort on the East Coast. The company will end up selling to a certain number of buyers in its target market

The penetrated market is the set of consumers who are buying the company's product" Philip Kotler (2006).

## 4.1 Valuation of existing market studies

The goal of this section is to find an expedient estimation of the market demand for EEG LI test and SIGFRIED, both of which can be part of the presurgical procedure for either brain tumor or epilepsy surgery. In the US, different associations represent different topics, and typically publish an annual report. This report usually contains statistical data and specific information about this field. The next subsections present data from :

- American Association of Neurological Surgeons **AANS**
- Association of American Medical College **AAMC**
- American Academy of Neurology **AAN**
- National Association of Epilepsy Centers **NAEC**
- National Brain Tumor Society **NBTS**
- Central Brain Tumor Registry of the United States **CBTRUS**

### 4.1.1 American Association of Neurological Surgeons AANS

In 2008 the AANS published an interesting survey that sought to outline the practice of neurosurgery in the United States in 2006. The survey questionnaire was sent to 4,482 neurosurgeons, 748 of whom returned it, which is a return rate of 17%. After the questionnaire was evaluated, the mean was calculated for the sample by each procedure audited. In 2006, 3,443 neurosurgeons were certified by the American Board of Neurological Surgery, so the procedural mean was multiplied by this number. Since a previous study was conducted in 1999, every table in the 2006 survey included information about trends. The only significant difference between the two surveys is that the latter survey differentiates categories based on the CPT codes, described in Section 6.2.2. In other words, every category consists of several specific CPT codes, and thus the content of the categories are very precisely defined.

The report contains data about physician and practice demographic profiles, procedures conducted in 2006, and other topics. Moreover, it includes an analysis and trend estimation as well as a “percentage performing” statistic. “Percentages were used in the 2006 and 1999 comparison columns. The “Percent Performing” statistics reflect the percentage of sampled neurosurgeons that performed each respective procedure. For example, of the 442 neurosurgeons whom responded to Spine/Laminectomy/Cervical, (63001, 63015, 63045) for 2006, 380 stated that they performed these cervical procedures, corresponding to 86.0% of the population sampled” American Association of Neurological Surgeons (2008). According to the report, the results should be accurate within five percentage points.

**Craniotomy for seizures** Table 4.1 on page 47 presents the number of lesion removal and mapping procedures performed. As mentioned earlier, the categories lesion

Craniotomy for Seizures	2006 Total Procedures	2006 % Performing	1996 % Performing
Lesion removal (61490, 61534, 61536 through 61543, 61566, 61567)	6,655	23.7%	12.5%
Mapping (61531, 61533, 61535, 61760)	5,084	15.7%	6.1%

Table 4.1: Number of performed lesion removal and mapping. “Both lesion removal and mapping consist of several CPT codes, which are listed in the tables 4.2 and 4.3” cf. American Association of Neurological Surgeons (2008).

removal and mapping both consist of several CPT codes, which are listed in the tables 4.2 and 4.3. The next two tables list the CPT codes for the categories lesion removal and mapping.

code	Description	Facility
61490	Craniotomy for lobotomy, including cingulotomy	\$1658.51
61534	Craniotomy with elevation of bone flap; for excision of epileptogenic focus without electrocorticography during surgery	\$1432.57
61536	Craniotomy with elevation of bone flap; for excision of cerebral epileptogenic focus, with electrocorticography during surgery (includes removal of electrode array)	\$2267.52
61537	Craniotomy with elevation of bone flap; for lobectomy, temporal lobe, without electrocorticography during surgery	\$2140.16
61538	Craniotomy with elevation of bone flap; for lobectomy, temporal lobe, with electrocorticography during surgery	\$2306.78
61539	Craniotomy with elevation of bone flap; for lobectomy, other than temporal lobe, partial or total, with electrocorticography during surgery	\$2059.44
61540	Craniotomy with elevation of bone flap; for lobectomy, other than temporal lobe, partial or total, without electrocorticography during surgery	\$1912.84
61541	Craniotomy with elevation of bone flap; for transection of corpus callosum	\$1876.43
61542	Craniotomy with elevation of bone flap; for total hemispherectomy	\$2007.77
61543	Craniotomy with elevation of bone flap; for partial or subtotal (functional) hemispherectomy	\$1884.40
61566	Craniotomy with elevation of bone flap; for selective amygdalo-hippocampectomy	\$1975.78
61567	Craniotomy with elevation of bone flap; for multiple subpial transections, with electrocorticography during surgery	\$2255.51

Table 4.2: CPT code for lesion removal. “The American Medical Association maintains the Current Procedural Terminology (CPT) codes, which describe medical, surgical, and diagnostic services, and the reimbursement process between physicians and insurance companies are based on the CPT code” Abraham and American Medical Association (2010).

code	Description	Facility
61531	Subdural implantation of strip electrodes through 1 or more burr or trephine hole(s) for long-term seizure monitoring	\$1058.47
61533	Craniotomy with elevation of bone flap; for subdural implantation of an electrode array, for long-term seizure monitoring	\$1327.38
61535	Craniotomy with elevation of bone flap; for removal of epidural or subdural electrode array, without excision of cerebral tissue (separate procedure)	\$862.78
61760	Stereotactic implantation of depth electrodes into the cerebrum for long-term seizure monitoring	\$1357.08

Table 4.3: CPT code for functional brain mapping. “The table lists all CPT codes, which describe medical, surgical, and diagnostic services, for the purpose of functional brain mapping. For functional brain mapping, the implantation of electrodes is a basic prerequisite. Also, SIGFRIED requires an implanted grid” Abraham and American Medical Association (2010).

**Procedure setting** The Table 4.4 on page 49 provides statistics about the different facilities where the surgeries were performed. This statistic shows that almost every

Facility	Percentage 2006	Percentage 1996
Hospital	95%	97%
Freestanding Surgical Center	3%	1%
Other	2%	N.A.
Office Facility	0%	1%

Table 4.4: Procedure setting. “National Neurosurgical Procedural Statistics from 2006 assess that 95% of the procedure settings are performed in a hospital environment. Especially for SIGFRIED, this number states that only hospitals perform functional brain mapping” American Association of Neurological Surgeons (2008).

procedure was performed in a hospital. We will use this result evaluate the number of hospitals that can perform functional brain mapping.

#### 4.1.2 Association of American Medical College AAMC

In the United States, medical schools have state of the art equipment and technologies, since their responsibility is to educate medical students. The most common way for medical schools to provide students with the best training environment is to collaborate with different medical hospitals, such as an epilepsy and brain tumor center. Furthermore, these collaborations provide opportunities for introducing new and/or high scientific technologies because of the unique combination of research, education and clinical practise. In other words, the medical schools are the target customers for SIGFRIED and EEG LI test and if the medical school contains both an epilepsy center and brain tumor center then it is most likely that the medical school purchases two products. Thus, the next two sections explains and assess the precise number of epilepsy and brain tumor centers, which have the knowledge to perform functional brain mapping.

Number	Item
133	Accredited M.D.-granting U.S. medical schools
17	Accredited Canadian medical schools
150	Total number of medical schools in the US and Canada

Table 4.5: “Number of medical schools in the US and Canada” Association of American Medical College (2010).

### 4.1.3 National Association of Epilepsy Centers NAEC

A epilepsy surgery (see Section 2.3.1) is a complex procedure, and hence many hospitals specialize in treating seizure disorders. In 1989, the National Association of Epilepsy Centers published the first set of guidelines for epilepsy centers under the title “Guidelines for essential services, personnel, and facilities in specialized epilepsy centers”. The last update is dated January 12 2010 and available through the homepage of the association ([www.naec-epilepsy.org](http://www.naec-epilepsy.org)). This guideline distinguishes between:

- Third–Level Medical Center for Epilepsy
- Fourth–Level Medical Center for Epilepsy

A third–level epilepsy center offers primary treatment and diagnostic services. The diagnostic services include noninvasive validation for a surgery, which could also consider EEG LI test. “In addition, many level 3 centers offer noninvasive evaluation for epilepsy surgery, straightforward resective epilepsy surgery and implantation of devices, such as the vagus nerve stimulator. Knowledge and experience with epilepsy surgery has become sufficiently widespread that lesionectomy and anterior temporal lobectomy in the presence of clear-cut mesiotemporal sclerosis can be performed at level 3 epilepsy centers” Labiner et al. (2010).

The more complex invasive functional brain mapping is performed exclusively at fourth–level epilepsy centers, because the surgery requires the best available conditions. Hence, the SIGFRIED technology would be operated only in level fourth centers. Moreover, the guideline provides a precise list of necessary specifications of provided services, personnel, outpatient video–EEG monitoring units, and inpatient units. In the appendix, the Table 9.1 on page 143 and Table 9.2 on page 144 contain a detailed description of the provided services with a focus on electrodiagnostic epilepsy surgery and imaging for a third and fourth level medical center. The next itemization outlines the provided services of a third level epilepsy center and is based on Labiner et al. (2010):

- Electrodiagnostic EEG services including long term monitoring
- Epilepsy Surgery including VNS (routine lesional surgeries and those not requiring invasive monitoring)
- Neuroimaging
- Neuropsychological and psychological services
- Pharmacological expertise

- Nursing support (specific to epilepsy)
- Rehabilitation (in patient and outpatient) including physical, occupational and speech therapy
- Consultative expertise in multiple fields: neurosurgery, psychiatry, internal medicine, pediatrics, general surgery, obstetrics/ gynecology

The next itemization shows the services that distinguish a fourth level epilepsy center from a third level epilepsy center and is based on Labiner et al. (2010):

- Functional cortical mapping by stimulation of subdural electrodes either extra-operatively or intraoperatively.
- Evoked potential recording capable of being used safely with intracranial electrodes.
- Electrocorticography.
- Placement of intracranial electrodes.
- Resection of epileptogenic tissue in the absence of structural lesions.
- Adequate clinical experience by both the neurosurgeon and neurologist/epileptologist.
- Specialized neuroimaging either on site or by established arrangement including interictal positron emission tomography (PET) and/or ictal single photon emission computed tomography (SPECT)

The database of the NAEC includes a list of all registered Epilepsy Centers in the US, and an outline is presented below in table 4.6.

Hospital	Number
Third-Level Medical Center for Epilepsy	12
Fourth-Level Medical Center for Epilepsy	115
Not attributed to a specific level	28
Total number of registered Epilepsy Centers	145

Table 4.6: Number of epilepsy centers. “The registered epilepsy centers are slitted into three categories and for SIGFRIED, the number of Fourth-Level Medical Center for Epilepsy can be counted as available market. On the other hand, the available market for EEG LI test includes all three categories” National Association of Epilepsy Centers (2010).

#### 4.1.4 National Brain Tumor Society NBTS

In addition to epilepsy centers, brain tumor treatment centers also benefit from the new technologies. Therefore, Table 4.7 concentrates on the number and size of brain tumor treatment centers in the US based on information provided by the National Brain Tumor Society (<http://www.brainumor.org>).

Hospital	Number
Brain Tumor Centers, that perform functional brain mapping	94
Brain Tumor Centers, that not perform functional brain mapping	31
Brain Tumor Centers, that provide no information whether the perform functional brain mapping	9
Total number of Brain Tumor Centers	134

Table 4.7: Number of Brain Tumor Centers. “The table categorizes the Brain Tumor Centers into three groups and for SIGFRIED, the number of Brain Tumor Centers, that perform functional brain mapping are suitable as available market. On the other hand, the available market for EEG LI test includes the total number of Brain Tumor Centers” National Association of Epilepsy Centers (2010).

At present, the society counts 134 brain tumor treatment centers in their database. The next pie diagram illustrate the sizes of the brain tumor treatment centers.

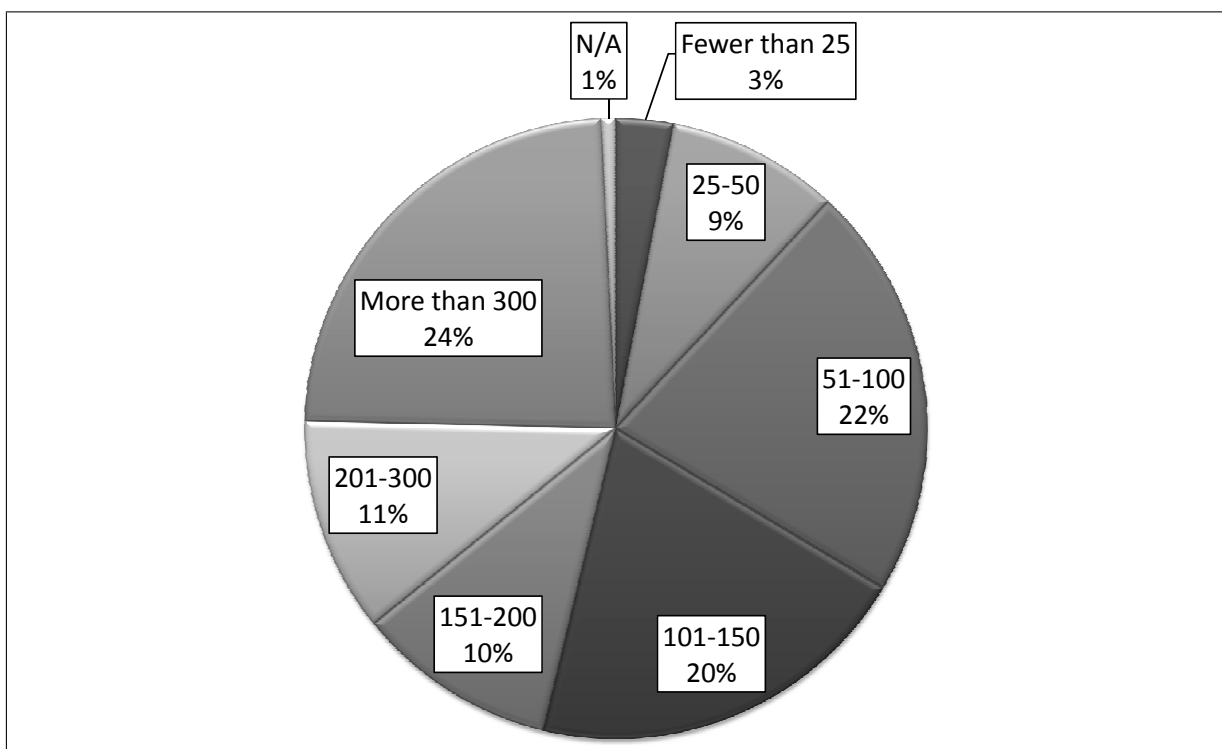


Figure 4.2: Contribution of performed brain surgery. The pie diagram shows the percentage of performed brain tumor surgeries per year at all 134 hospitals. For example, 24 per cent of all Brain Tumor Centers operate more than 300 patients per year.

The diagram is based on the number of performed brain surgeries at each hospital per year and these numbers are categorized in eight groups: Fewer than 25, 25–50, 51–100, ..., more than 300 brain surgeries performed per year. The percentage number represents the treatment center quantity of each category divided by the total number of brain tumor treatment centers.

#### 4.1.5 Central Brain Tumor Registry of the United States CBTRUS

The CBTRUS published a statical report with the title: *“Primary brain and central nervous system tumors diagnosed in the United States in 2004–2006* and Figure 4.3 on page 53 is a part of this report.

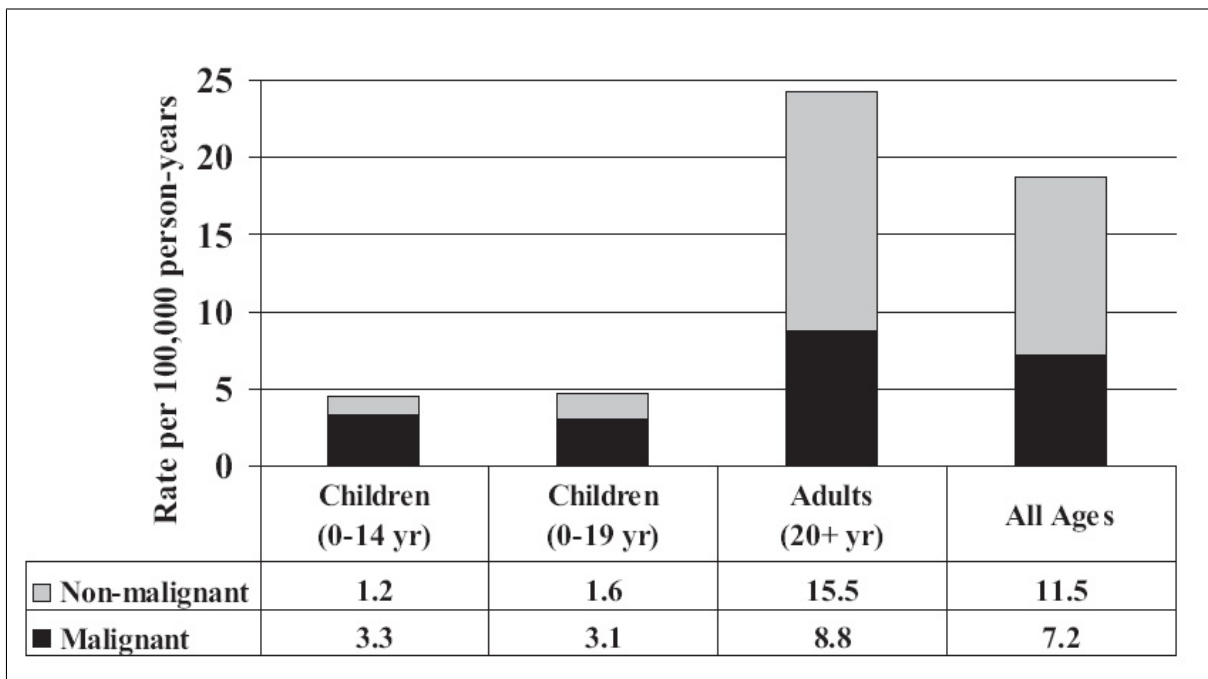


Figure 4.3: Incidence rate of brain tumor per year. “Average annual age-adjusted incidence rates, age-adjusted to the 2000 United States standard population, of primary brain and CNS tumors by age and behavior. In general, functional brain mapping is difficult to perform at children, because the brain functions’ location changes during the childhood” Kruchko (2010).

“CBTRUS expects 62.930 new cases of primary non–malignant and malignant brain and central nervous system tumors to be diagnosed in the United States in 2010” Kruchko (2010). The Figure 4.3 on page 53 shows the compares incidence rate between children and adults. In general, the knowledge about functional brain mapping in children limited, because the location of the brain functions changes during childhood and the changing process is not well explored. Thus every established methods has limitation in functional brain mapping for children.



#### 4.1.6 American Academy of Neurology AAN

The following chart lists the number of AAN members in each category in 2009 and 2008. Each total represents membership as of December 31. Because EEG-based

AAN Members Category	Year 2008	Year 2009
Active (certified by qualifying board)	9782	9668
Junior (In training)	3596	3878
Associate(Not certified by qualifying board)	2579	2741
Fellow (elected based on contributions)	1702	1741
Senior (Retired or disabled)	1258	1326
Students (Medical and PhD candidate students)	1305	1536
Corresponding Active (Certified outside of US and Canada)	563	666
Non-physician neurology professionals	933	1083
Corresponding Fellow (Outside the US/Canada elected based on contributions)	269	253
Honorary (elected based on meritorious contributions)	66	65
Total number of American Academy of Neurology's Members	22053	22957

Table 4.8: AAN Members. "The chart lists the number of American Academy of Neurology members in each category in 2009 and 2008" American Academy of Neurology (2010).

technologies are safe and easy to use, it can be performed at the doctor's practice. After EEG LI test is established in medical schools, the available market for EEG LI test expands to the 9668 active neurologies.

## 4.2 Summary of development results' available market

Based on the information from the four associations presented above, this section ascertains the market demand for both recently developed clinical diagnostic tests SIGFRIED and EEG LI test. The aim of this thesis is to assess whether these development results are economically meaningful. Hence, a detailed market study is not currently necessary. This section and the following section evaluate the available market for the two new technologies, because this is the most significant number for the next step of the innovation process. The available market contains two numbers. The first is the number of annually performed procedures. The second number is the quantity of hospitals and doctors who meet the categories of the available market.

**Market demand of SIGFRIED** The SIGFRIED method only can be utilized for patients who have a grid implanted. Furthermore there must be a medical need to localize of brain functions. Hence, the available market can be estimated based on the number of patients who get the grid implanted for purpose of brain mapping. Based on

CPT codes, the section Section 4.1.1 identifies the number of functional brain mapping, which is the available market for SIGFRIED, as following:

In the year 2006 brain mapping was performed **5,084** times.

The next table lists the quantity of hospitals that perform functional brain mapping, which include the Fourth–level Epilepsy Centers (see Section 4.1.3), and Brain Tumor Treatment Center that execute functional brain mapping (see Section 4.1.4).

Medical Centers that perform functional brain mapping	Number
Fourth–Level Medical Center for Epilepsy	115
Brain Tumor Center that perform functional brain mapping	94
Available market demand for SIGFRIED	<b>209</b>

Table 4.9: Available market of SIGFRIED. The Table lists all hospital, which perform functional brain mapping. Thus the sum of them is the available market for SIGFRIED.

**Market demand of EEG LI test** The market demand for EEG LI test is much larger than for SIGFRIED for two reasons. First, EEG LI test is non invasive, and thus there no concerns about the patient’s safety. Second, EEG is a widely used technology that is less expensive that invasive alternatives. In the interview (see Section 4; paragraph Target customer),Dr. A.L. Ritaccio said that every new patient is evaluated with EEG measures once, and it would reasonable to do a EEG LI test for epileptic and brain tumor patients. In other words, the available market can be estimated based on the number of new epileptic and brain tumor patients per year.

Patients, who benefit from EEG LI test	Number
New cases of epilepsy (see Section 2.3.1)	181,000
New cases of primary non–malignant and malignant brain and central nervous system tumors (see Section 4.1.5)	62,930
Sum of new cases of epilepsy and brain and central nervous system tumors	<b>243,930</b>

Table 4.10: Incidence rate of epilepsy and brain tumor. Per year, all this patients would benefit from the EEG LI testin the United States.

As mentioned above, all specialized Medical Center in epilepsy and brain tumor are the available market for EEG LI test and the Table 4.11 lists them.

Medical Centers that perform language lateralization	Number
All Epilepsy Centers	145
All Brain Tumor Centers	134
Available market for EEG LI test	<b>279</b>

Table 4.11: Available market of EEG LI test as a pre-surgical procedure for brain surgery. The Table lists the hospital, which are considered as available market for EEG LI test at the introduction phase. When the technique is established in the hospitals, than the available market will expand to private physicians.

According to Dr. Ritaccio, the available market for EEG LI test as a neurological assessment battery is provided in Table 4.12.

Hospital and physicians that benefit from EEG LI test	Number
Active certified AAN members)	9782
All Epilepsy Centers	145
All Brain Tumor Centers	134
Available market for EEG LI test as a neurological assessment battery	<b>10,061</b>

Table 4.12: Available market of EEG LI test as a neurological assessment battery. The Table lists the hospital, which are considered as available market for EEG LI test at the introduction phase. When the technique is established in the hospitals, than the available market will expand to private physicians.

The available market for EEG LI test as a neurological assessment battery is approximately 35 times larger than as a presurgical procedure for brain surgery.

# 5 Regulatory environment of a medical device in US

This chapter explain and form the statutory framework pertaining to software in a BCI system. In the United States are different types of certification necessary during the innovation process that must be considered. We discuss in this chapter the regulatory environment and the subsequent chapter deals with reimbursement process. The chapter 7 focuses on the purchasing-decision process between the development result's manufacturer and the hospital, which is the last step at the innovation process. There are three big organizations that play a major role in regulatory environment and reimbursement process, and they are listed below. The documentation for both topics may overlap or correspond to each other and furthermore, working on both applications simultaneously saves time.

1. Food and Drug Association (FDA)
2. Centers for Medicare & Medicaid Services (CMS)
3. American Medical Association (AMA), in particular Current Procedural Terminology (CPT)

The FDA's (see Section 5.2) responsibility is to ensure the safety and effectiveness of any medical device to be launched, and thus each medical device needs an FDA approval certificate to be distributed in the United States. The Centers for Medicare & Medicaid Services are the biggest health insurers in the United States: they decide if the new treatment is reimbursed by them, and most other insurance companies follow their decision. The determination hinges on claims of cost-effectiveness and clinical effectiveness rather than on safety concerns, because these are already checked by the FDA. The next step is to obtain a reimbursement code for the billing system of the hospital and private physician. The CPT codes are administrated by the AMA and the code itself has an impact on the amount that can be reimbursed for the treatment. A high reimbursement value is one key element in the customers' purchasing decision

process Raab and Parr (2006c), and in the chapter 7, we look into the purchasing decision of a hospital. In particular, we point out the position of the different decision-making units (DMU) and the relevant factors of influence.

The regulatory environment comes into play during the implementation phase of the innovation process, because the first safety concerns occur at the testing phase. The FDA strives to be involved very early in the innovation process, and Figure 5.1 displays the time line of the recommended collaboration. This document is organized in the order of the milestones presented in Figure 5.1 on page 58. The first chance to contact

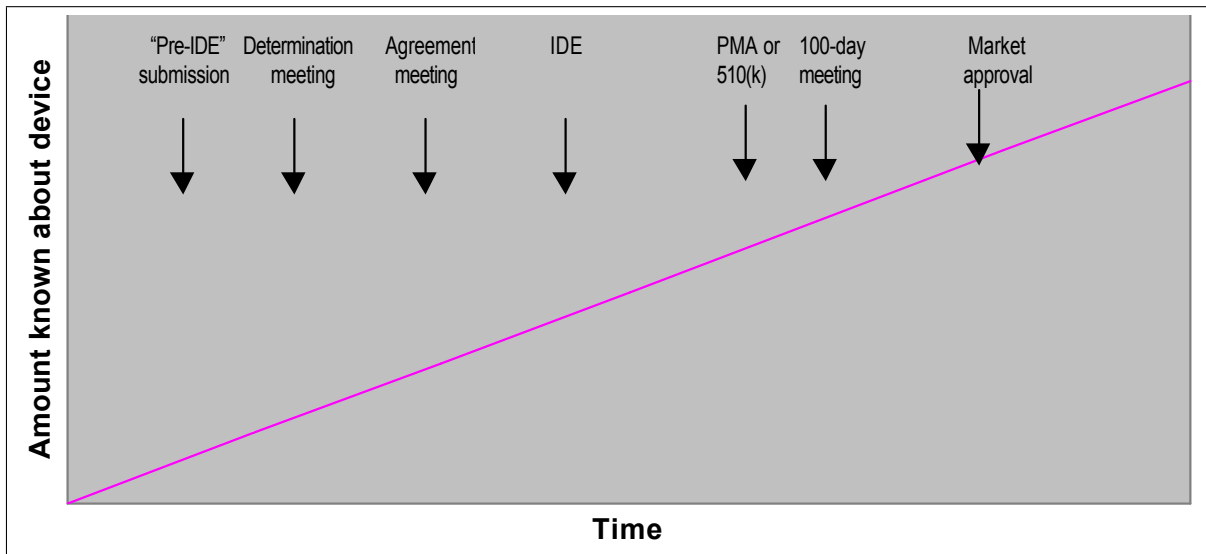


Figure 5.1: Market approval time line. “Graphical illustration of a typical approach to communication about a new device. Vertical arrows illustrate typical timing of potential communications between the sponsor and the Agency. The x-axis represents the device development time line, while the y-axis represents the amount known about the device” Food and Drug Administration (2001).

the FDA is the Pre-IDE Process (IDE stands for Investigational Device Exemption and is explained in Section 5.1), which is especially recommended for either new sponsor or novel technologies. The early corporation should speed up the whole application process and support the understanding of the FDA regulations. There are two possible mechanisms for the inventor and FDA to communicate:

1. Pre-IDE meeting
2. Pre-IDE submission

Further information about the Pre-IDE Process is provided on the homepage of the FDA ([www.fda.gov](http://www.fda.gov)). The next two milestones in the time line are the determination meeting and agreement meeting.

**Determination meeting** According to the FDA: “A Determination Meeting is available to anyone anticipating submitting a PMA (see Section 5.2.1) and is intended to provide the applicant with the Agency’s determination of the type of valid scientific evidence that will be necessary to demonstrate that the device is effective for its intended use. Based on this meeting, the FDA will determine whether clinical studies are needed to establish effectiveness and, in consultation with the applicant, determine the least burdensome way of evaluating device effectiveness that has a reasonable likelihood of success” cf. Food and Drug Administration (2001).

**Agreement meeting** The FDA describes the agreement meeting as : “The other opportunity for a meeting established by FDA is an Agreement Meeting, which is open to any person planning to investigate the safety or effectiveness of a class III (see Section 5.2) product or any implant. Thus, unlike the Determination Meeting, the Agreement Meeting is available to submitters of 510(k)s (see Section 5.2.2 for eligible devices. The purpose of this meeting is to reach agreement on the key parameters of the investigational plan, including the clinical protocol” cf. Food and Drug Administration (2001).

## 5.1 Investigational Device Exemption

To execute a clinical study, an investigator must have approval for Investigational Device Exemption (IDE). This approval must be issued before the clinical study takes place. However, a clinical study is required for a Premarket Approval (PMA) (see Section 5.2.1) application and for a few Premarket Notification 510(k) (see Section 5.2.2) submissions, but there could be also other motives for a clinical study American Medical Association (2009b). The IDE rules differentiate between significant and nonsignificant risk device studies. IDE’s for a significant risk study must be submitted to the FDA. However, FDA regulations allow an Institutional Review Board (IRB) to act in FDA’s stead for non-significant risk studies. So if you presented your investigational plan, informed consent forms, etc. to the IRB, and the IRB concluded that it was a nonsignificant risk device studies (NSR) study, you in effect have an “approved” IDE. The majority of IDE’s are NSR, and the FDA does not know about them until a firm submits a premarket submission to the agency. Thus, the data gathered under your IDE is to support the safety and effectiveness of the device and will be included in the premarket approval submission, if one is required. The Flowchart in Figure 5.2 on page 60 summarize the whole IDE application process.

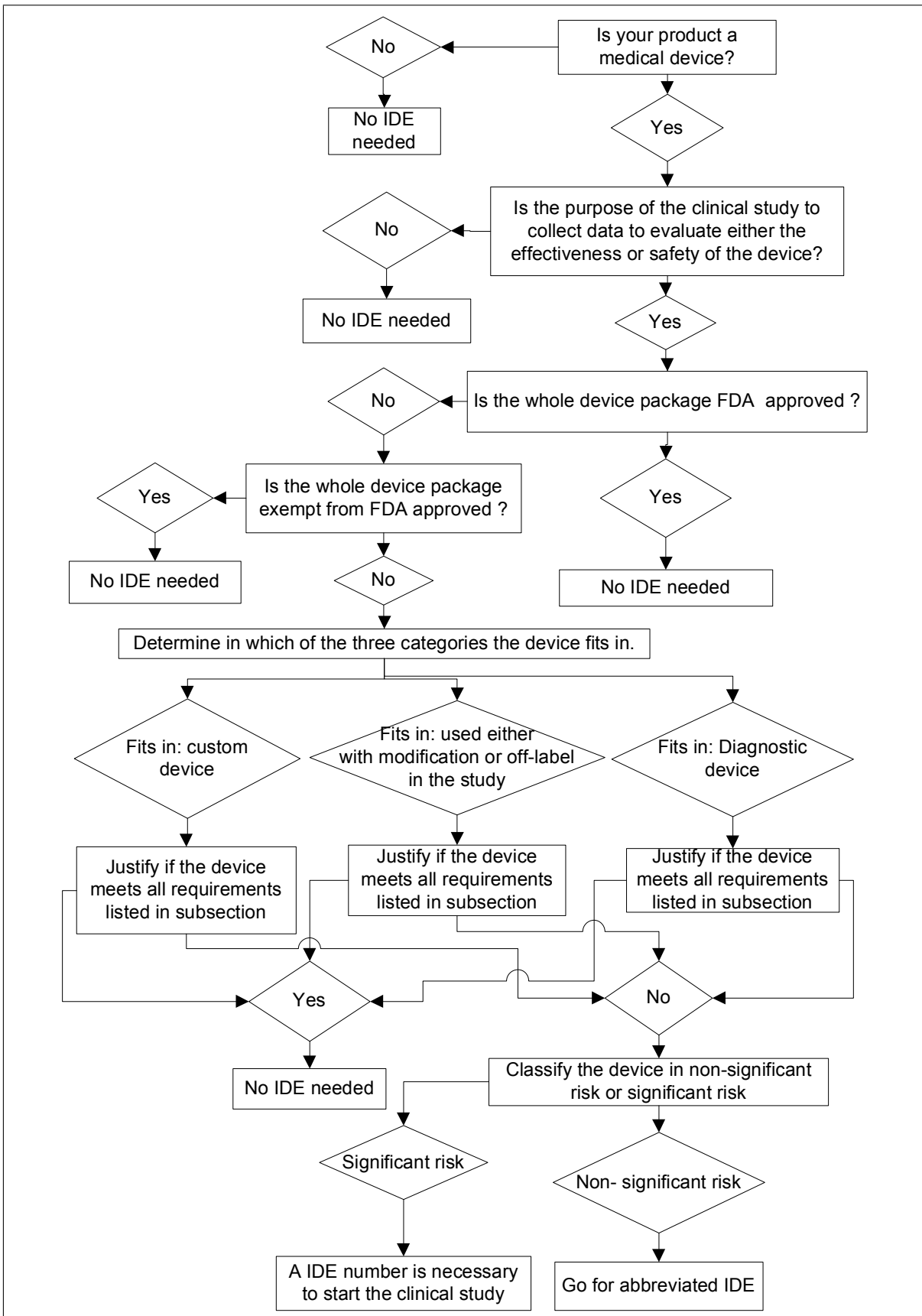


Figure 5.2: Flowchart IDE. Graphical illustration of the Investigational Device Exemption submission process.

For the purposes of assisting the Center of Medicare & Medicaid Services (see Section 6.1) in determining Medicare coverage, the FDA will place all approved IDEs in one of two categories:

**Category A:**“Experimental - Innovative devices believed to be in class III for which absolute risk of the device type has not been established (i.e., initial questions of safety and effectiveness have not been resolved, and the FDA is unsure whether the device type is safe and effective)” cf. Center of Medicare & Medicaid Services (2010).

**Category B:**“Nonexperimental and/or investigational devices believed to be in classes I or II, or devices believed to be in Class III, where the incremental risk is the primary risk in question (i.e., underlying questions of safety and effectiveness of that device type have been resolved), or it is known that the device type can be safe and effective because, for example, other manufacturers have obtained FDA approval for that device type” Center of Medicare & Medicaid Services (2010).

## 5.2 Food and Drug Administration

The Food and Drug Administration (FDA) takes care of public health in the United States through supervision and regulations. It is a part of the United States federal executive department of Health and Human Services, headquartered in Rockville, Maryland. One of the agency’s responsibilities is the regulatory environment for medical devices and the certification of devices for the US market. Every medical device needs an FDA approval certification before it can be commercially sold in the US. “The FDA estimates that more than 8,000 new medical devices are marketed each year in the United States” Raab and Parr (2006a). This section highlights the effective regulations for software used in a BCI systems and in particular for the two clinical diagnostic tests SIGFRIED and EEG LI test. First all relevant regulations for both tests are discussed in general and then Section 5.3 shows in detail what the submitter must do for a successful application. The regulations are split into two parts and are organized in the following order.

1. Guidelines for medical devices in general
2. Guidelines for software used in context of medical devices

Each part is based on information provided by the Food and Drug Administration. Generally, there are two types of documents published by the FDA. First, title 21 of the Code of Federal Regulations (CFR) contains all rules of the Food and Drug Administration and is promulgated in the Federal Register by agencies of the Federal Government



and the Executive departments. In this work, we use the term 21 CFR to reference this text of law. Second, the FDA releases guidance documents, which represent the Agency's current thinking, but are not legally binding. In other words, the 21 CFR is the text of a law and difficult to understand for a layman, so the FDA provides further explanations in form of guidance documents. Most of the citations in this chapter are the from guidance documents, and they are marked as usual.

Before we describe the regulations for a medical device in detail, we have to talk about the term "medical device". Hence, the first question is: does the FDA consider the diagnostic tests as an medical device? A medical device is defined as:

"an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is" Food and Drug Administration (2010c):

- "recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them" Food and Drug Administration (2010c),
- "intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or" Food and Drug Administration (2010c)
- "intended to affect the structure or any function of the body of man or other animals, and which does not achieve any of it's primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes" Food and Drug Administration (2010c).

However, if the definition is not precise enough to categorize the development result, then a look into the "CDRH product classification database" can give you support. This database contains all medical devices with a short description and is only available at the Web site <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpcd/classification.cfm>. If an almost similar device is listed in the database, it is predictable that the development result will also be considered a medical device. The final method for answering this question is to contact the FDA.

**Guidelines for medical devices in general** The FDA distinguishes between two principal routes for marketing approval, and the classification for one route has a large impact on the further marketing approval application process.

1. Premarket notification (510k) is available for development results that are considered "substantially equivalent" (see 5.2.2 for a precise definition) to an already legally launched class I or II medical device.

2. Pre-marketing approval process (PMA) is required for all class III medical devices and for novel devices which are "not substantially equivalent" to existing medical devices legally launched on the market.

Class I, II and III medical devices are discussed in the next section.

**Medical device classification** The FDA uses three categories, class I to III, to classify a medical device, and this classification affects the scope and nature of the approval process. The classification depends on the:

- intended use
- indications for use
- the risk the device poses to the patient

A class I medical device has the lowest safety concerns and a class III has a highest concerns. The fastest way to find out in which class a development result fits is to look for a similar device in the already mentioned "CDRH product classification database" of the FDA. The database is organized in parts with the official reference numbers 21 CFR 862 through 892. 21 CFR stands for Title 21 of the Code of Federal Regulations (CFR), and (for example) 862 defines the part "Anesthesiology". As mentioned earlier, everyone who wants to launch a class III device, or a novel device for human use, has to obtain Premarket Approval. Novel in this context means that it is not possible to find an already-approved "substantially equivalent" device. By default, any novel device is treated at the same risk level as class III device. However, a novel medical device manufacturer can go for a "Evaluation of automatic class III designation provision" (see section 5.2.2) if the safety concerns of the novel device would fit into class I or II. Devices for which a "substantially equivalent" medical device for human use can be found require a 510(k) certification, unless exempt from it. The PMA has a lengthier submission process than a 510(k) approval process and the Sections 5.2.1 and 5.2.2 explain both application procedures in detail.

### **5.2.1 Premarket approval (PMA)**

All class III medical devices need to apply for the PMA, which it is the most strict approval process. "Fewer than 100 of the 8,000 new medical devices that come to market in the United States in any given year undergo full "premarket approval" review to determine their safety and effectiveness" Raab and Parr (2006a). The application has to be supported by much data. The FDA provides a description of the required information on the Web site and the next paragraphs are cited from the FDA.

**Data Requirements** “A Premarket Approval (PMA) application is a scientific, regulatory documentation to the FDA to demonstrate the safety and effectiveness of the class III device. There are administrative elements of a PMA application, but good science and scientific writing are key to the approval of a PMA application. If a PMA application lacks elements listed in the administrative checklist, the FDA will refuse to file a PMA application and will not proceed with the in-depth review of scientific and clinical data. If a PMA application lacks valid clinical information, and appropriate scientific analysis based on sound scientific reasoning, it will delay FDA’s review and approval. PMA applications that are incomplete, inaccurate, inconsistent, omit critical information, and/or poorly organized have resulted in delays in the approval or denial of PMA applications. Manufacturers should perform a quality control audit of a PMA application before sending it to FDA to assure that it is scientifically sound and presented in a well organized format” Food and Drug Administration (2010d).

**Technical sections:** “The technical sections containing data and information should allow the FDA to determine whether to approve or disapprove the application. These sections are usually divided into non-clinical laboratory studies and clinical investigations” Food and Drug Administration (2010d).

**Non-clinical laboratory studies’section:** “Non-clinical laboratory studies’ section includes information on microbiology, toxicology, immunology, biocompatibility, stress, wear, shelf life, and other laboratory or animal tests. Non-clinical studies for safety evaluation must be conducted in compliance with 21CFR Part 58 (Good Laboratory Practice for Nonclinical Laboratory Studies)” Food and Drug Administration (2010d).

**Clinical investigations’section:** “Clinical investigations’ section includes study protocols, safety and effectiveness data, adverse reactions and complications, device failures and replacements, patient information, patient complaints, tabulations of data from all individual subjects, results of statistical analysis, and any other information from the clinical investigations. Any investigation conducted under an Investigational Device Exemption (IDE) must be identified as such” Food and Drug Administration (2010d).

The last paragraphs showed that a PMA is both very time consuming and expensive. Therefore, a company should decide very carefully whether it makes sense to apply for PMA for a given development result. For both research outcomes, a less time-consuming premarket notification should be the goal.

## 5.2.2 Premarket notification

A medical device is qualified for the premarket notification (510k) application process if it is exempt from a PMA process. Typically this is the case for a class I and II medical device, but there also a few class III devices that qualify for the premarket notification. The next paragraphs deal with the different submission process methods and address when you have to submit 510k. First, we will explain in more detail when the premarket notification is applicable for a new medical device.

The goal of every 510k application is to receive a letter from the FDA that judges a device as “substantially equivalent”, because this letter allows the submitter to market the device in the United States. The term “substantially equivalent” plays a major role in the 510(k) application process. The idea behind the 510(K) application process is to demonstrate that the new device is as safe as an already approved medical devices. “substantially equivalent” is defined as follows based on Food and Drug Administration (2010e):

- has the same intended use as the predicate; **and**
- has the same technological characteristics as the predicate; **or**
- has the same intended use as the predicate; **and**
- has different technological characteristics and the information submitted to FDA;
  - does not raise new questions of safety and effectiveness; **and**
  - demonstrates that the device is at least as safe and effective as the legally marketed device

Hence an inventor can submit a premarket notification if his innovation is not categorized as class III and he can find a “substantially equivalent” approved medical device. The FDA can also refuse the submission with the reason that they define the device as “not substantially equivalent”. We discuss this scenario in the paragraph “Evaluation of automatic class III designation provision”(5.2.2).

In the last paragraph we assumed that we have a novel device, but the regulatory environment for a change or modification of an existing device is another matter. The FDA requires a 510 k submission for the following cases:

- “You propose a different intended use for a device which you already have in commercial distribution. The 510(k) regulation (21 CFR 807) specifically requires a 510(k) submission for a major change or modification in intended use. Intended use is indicated by claims made for a device in labeling or advertising. Most, if not

all changes, in intended use will require a 510(k). Please note that prescription use to over the counter use is a major change in intended use and requires the submission of a new 510(k)” Food and Drug Administration (2010e).

- “There is a change or modification of a legally marketed device and that change could significantly affect its safety or effectiveness. The burden is on the 510(k) holder to decide whether or not a modification could significantly affect safety or effectiveness of the device. Any modifications must be made in accordance with the Quality System regulation, 21 CFR 820, and recorded in the device master record and change control records. It is recommended that the justification for submitting or not submitting a new 510(k) be recorded in the change control records” Food and Drug Administration (2010e).

In our case, we may be classified as a “change or modification of a legally marketed device” and the FDA published the guideline *“Deciding When to Submit a 510(k) for a Change to an Existing Device”* to provide additional information. In this guideline, the section *“Is it a change in software or firmware?”* deals with software changes and the following itemization is based on Food and Drug Administration (1997).

- Does the change affect the indications for use? As with an explicit labeling change, if the change affects the indications for use, i.e., if it creates an implied new indication for use, then a new 510(k) should be submitted.
- Are clinical data necessary to evaluate safety and effectiveness to determine substantial equivalence? Whenever a manufacturer recognizes that clinical data are needed because bench testing or simulations are not sufficient to assess safety and effectiveness, and thus to establish the substantial equivalence of a new design, a 510(k) should be submitted. In the case of in vitro diagnostic devices, however, clinical samples may be collected and analyzed to demonstrate that the device continues to conform to performance specifications as contained in a voluntary standard or as described in a previous 510(k). A new 510(k) is normally not necessary in this situation.
- Do results of design validation raise new issues of safety and effectiveness? All changes to device design will require some level of design validation or evaluation to assure that the device continues to perform as intended. The successful application of routine design validation activities will logically result in manufacturers documenting their efforts and proceeding with the design change, i.e., assuring that no issues of safety or effectiveness are raised. Occasionally, however, either routine design validation activities produce unexpected results or otherwise

prove to be inadequate to validate the design change. In such instances, questions of safety and effectiveness may be associated with the design change, and the manufacturer may need to submit a new 510(k).

Now we know when we have to submit a 510k, and hence the next step is to look more closely at the submission process itself and at the different submission methods.

### **510k submission methods**

The FDA recently developed the new 510k paradigm that offers two additional submission methods to the established traditional 510k.

1. Traditional 510k
2. Special 510k
3. Abbreviated 510k

The workflow diagram below gives an overview of the three submission methods and the next paragraphs discuss them in more detail.

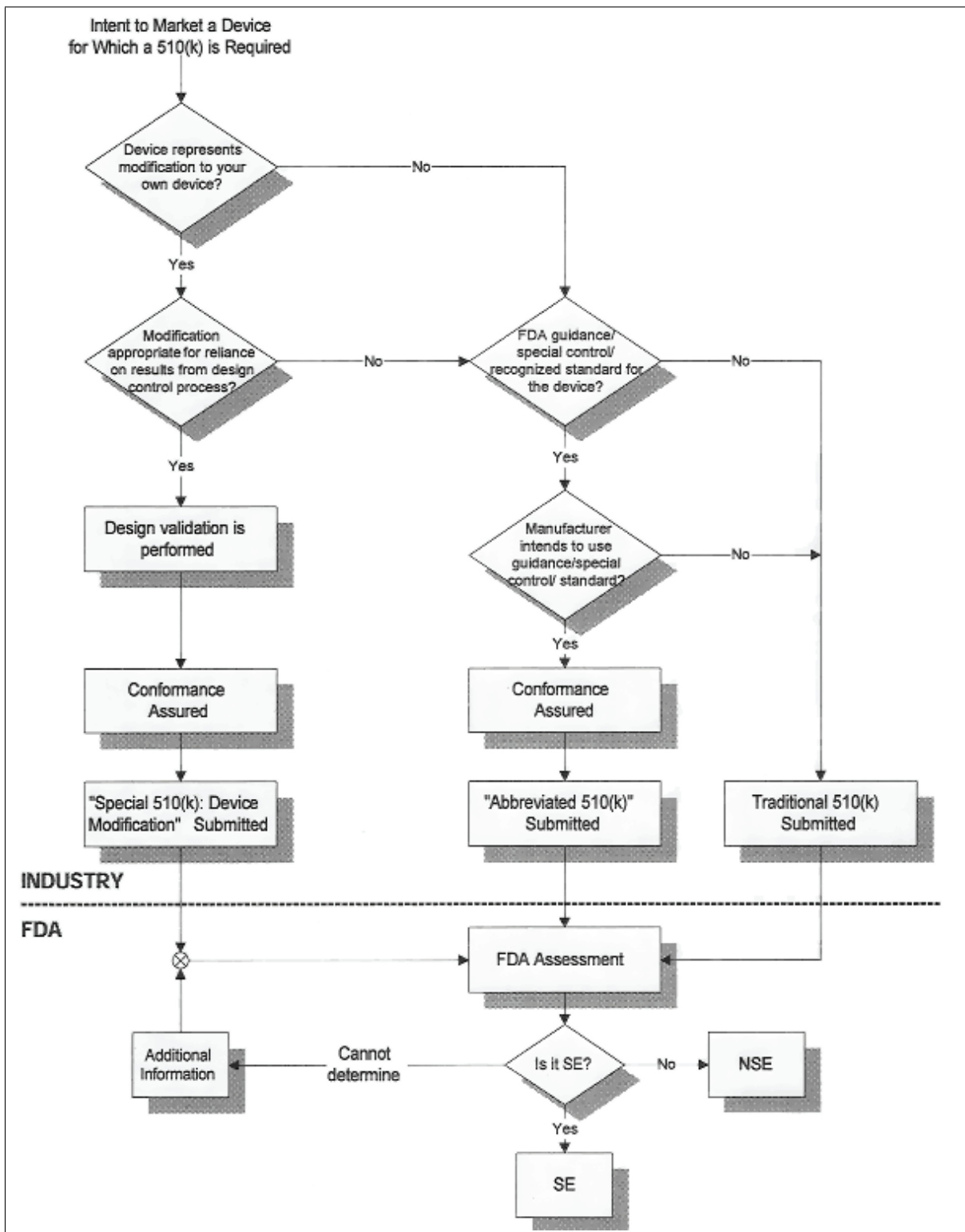


Figure 5.3: 510(k) submission methods. “The flowchart diagram displays the 510k paradigm, which splits up into three types: Special, Abbreviated and Traditional. Every 510k application is based on a “Substantially Equivalent” (SE) device” Food and Drug Administration (2010a).

Before the different methods are explicated in particular, we present some general guidelines that apply to all types. Based on Food and Drug Administration (2010b), the article “content of a 510k”, which contains a list of the necessary elements that a submitter needs up front

1. Classification of your device
2. Predicate device(s)
3. Final draft labeling
4. Specifications including engineering drawings, photos, etc.
5. Performance data such as bench, animal, or clinical testing (if applicable)
6. Sterilization information (if applicable)
7. Guidance document(s) specific to your device type, if it exists

When writing the application, you should ensure that the data are presented in a logical order, and that the data analysis exhibits appropriate scientific rigor. The application should also show why the test program makes sense, and should include a complete summary of the test results. The content of the application should be organized in the following order, based on Food and Drug Administration (2010b):

1. Table of Contents
2. 510(k) Screening Checklist
3. Statement of Indications for Use
4. 510(k) Statement or Summary
5. Truthful and Accuracy Statement
6. Proposed Labeling
7. Specifications
8. Substantial Equivalence Comparison
9. Performance



As mentioned earlier, the article “content of a 510k” Food and Drug Administration (2010b) provides a definite description of each single component of the context. Also the article “510(k) Format Tips” gives support to write an application and is also available on the FDA webpage. In this section, we concentrate on the regulatory environment for a BCI system, with particular focus on the regulations for software used in a BCI system. The article “Special Considerations” in the context of premarket notification expresses the current thinking of the FDA on this topic, and the paragraph below is cited from this article.

“If the device contains software or is controlled by a computer, the submission should contain documentation of software development and validation appropriate to the level of risk of the software. The submission should include any information, prompts, and cautions displayed by the system. The software documentation should support all performance and safety claims” Food and Drug Administration (2010b).

The following guidance documents provide guidance on the recommended software documentation for a premarket submission and on software validation.

1. Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices
2. General Principles of Software Validation
3. Guidance for Off-the-Shelf Software Use in Medical Devices
4. Cybersecurity for Networked Medical Devices Containing Off-the-Shelf (OTS) Software

These four guidance documents are explained in the section 5.2.3, and we now address the three submission methods.

**Traditional 510k** The FDA provides the following explanation: “The Traditional 510(k) method can be used under any circumstances. There is no Premarket Notification 510(k) “form” to complete. A 510(k) is a document containing information required under 21 CFR 807 Subpart E. All 510(k)s are based on the concept of substantial equivalence (SE) to a legally marketed (predicate) device. All 510(k)s provide a comparison between the device to be marketed and the predicate device or devices” Food and Drug Administration (2009a)

**Special 510(k): device modification** If a device modification does not affect the intended use or alter the fundamental scientific technology of the device, the manufacturer qualifies for the “Special 510k” application. The “Special 510k” requires less documentation than the traditional 510k.

**Abbreviated 510(k)** The FDA provides the manufacturers a shorter premarket notification application process for medical devices, where already recognized standards, guidance documents and special controls are established. However, the submission must contain the elements represented in 21 CFR 807.87, but under certain conditions, test data may not be necessary for an FDA approval certification. The FDA recommends the abbreviated 510(k) for the following circumstances.

1. a guidance documents exists
2. a special control has been established, or
3. FDA has recognized a relevant consensus standard.

The application should include an explanation for the circumstance above used.

**Evaluation of automatic class III designation provision** At the beginning of this subsection, we define the goal of the 510k to receive a letter from the FDA which determines the device as “substantially equivalent”. But what can be done if you the letter says that the FDA considers our device as “not substantially equivalent” (NSE)? This letter places automatically the device into class III. Then, the inventor has two options:

1. to apply for a premarket approval (PMA) or
2. to apply for “Evaluation of automatic class III designation provision” also know as “de novo reclassification”

The PMA application is discussed in the section 5.2.1, and we now address the second option because it is very realistic for our innovative diagnostic tests. After receiving the NSE letter, the submitter has 30 days to request a risk-based classification determination. This request must include a statement that points out that the device is entitled for a lower medical device class than level III. Within sixty days, the FDA responds on the request and decides the class. If the FDA concludes that the device is suitable for class I or II the submitter can go for a 510k application. The “de novo reclassification” has many advantages and disadvantages, and we will first address the positive aspects. A 510k application is less extensive, and the requirements after commercialization are less onerous. Second, the approval process is lighted for iterations and upgrades, but on the other hand the reclassification helps competitive companies to launch a “substantially equivalent” device. A PMA approval requires more stringent review and testing. Hence, this procedure could improve the product, and also helps to protect from liability. The inventor has to decide which aspect is more important for the overall goal of the company.

### 5.2.3 Software in the context of medical device

Both recently developed diagnostic tests SIGFRIED and EEG LI test contain novel signal processing software (see chapter 3). In our case, we use an already FDA approved device for the signal acquisition (see Section 2.1.1 and Figure 2.2 on page 10), which consists of hardware and software. Hence there are two possible scenarios to obtain FDA approval for both tests.

Scenario I: to cooperate with a signal processing device manufacturer and sell the diagnostic test as an upgrade of the existing software operating system.

Scenario II: to sell the clinical diagnostic test as stand alone software.

In both cases, an FDA approval certificate is required, and the FDA published four guidelines related to software in the field of medical device, which are named in Section (5.2.2). These guidance documents are explained in the following subsection, and we highlight the important information for the two development results.

#### **Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices**

Based on Food and Drug Administration (2005), the content of this guideline fits for the following products:

- firmware and other means for software-based control of medical devices
- stand-alone software applications
- software intended for installation in general-purpose computers
- dedicated hardware/software medical devices.
- accessories to medical devices when those accessories contain or are composed of software.

This guidance is valid for Premarket Notification (510k) (including Special, Traditional and Abbreviated), Premarket Approval Application and Investigational Device Exemption. "This guidance applies to software devices regardless of the means by which the software is delivered to the end user, whether factory-installed, installed by a third-party vendor, or field installed or upgraded" Food and Drug Administration (2005).

**Level of Concern** The FDA distinguishes between major, moderate or minor level of concern, which is not related to the medical device classification (see 5.2). The level of concern makes an huge impact on volume of the application process, and therefore

the application documentation should explain the level used. The FDA provides several questions which support the determination of the level of concern and the relevant ones for a BCI product are listed below.

“If the answer to the question below is Yes, the Level of Concern for the Software Device is likely to be **Major**.

*Does the Software Device provide diagnostic information that directly drives a decision regarding treatment or therapy, such that if misapplied it could result in serious injury or death? Is the Software Device an accessory to a medical device that has a Major Level of Concern?*

If the answer to the question below is Yes, the Level of Concern for the Software Device is likely to be **Moderate**.

*Could a malfunction of, or a latent design flaw in, the Software Device lead to an erroneous diagnosis or a delay in delivery of appropriate medical care that would likely lead to Minor Injury? Is the Software Device an accessory to a medical device that has a Moderate Level of Concern?*

If the answers the above questions are No, the Level of Concern is **Minor**” Food and Drug Administration (2005).

The determination of the level of concern should be clear before the investor moves on with the next steps. Therefore, if any doubts are left, the inventor should contact the FDA. The table 5.4 shows the required documentation for minor, moderate and major levels of concern based on the document “Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices”. This guidance also provides more information for each element in the list and this guideline also recommends risk management, which is explained in Section 5.2.3.

<b>SOFTWARE DOCUMENTATION</b>	<b>MINOR CONCERN</b>	<b>MODERATE CONCERN</b>	<b>MAJOR CONCERN</b>
Level of Concern	A statement indicating the Level of Concern and a description of the rationale for that level.		
Software Description	A summary overview of the features and software operating environment.		
Device Hazard Analysis	Tabular description of identified hardware and software hazards, including severity assessment and mitigations.		
Software Requirements Specification (SRS)	Summary of functional requirements from SRS.	The complete SRS document.	
Architecture Design Chart	No documentation is necessary in the submission.	Detailed depiction of functional units and software modules. May include state diagrams as well as flow charts.	
Software Design Specification (SDS)	No documentation is necessary in the submission.	Software design specification document.	
Traceability Analysis	Traceability among requirements, specifications, identified hazards and mitigations, and Verification and Validation testing.		
Software Development Environment Description	No documentation is necessary in the submission.	Summary of software life cycle development plan, including a summary of the configuration management and	Summary of software life cycle development plan. Annotated list of control documents generated during development process. Include the

<b>SOFTWARE DOCUMENTATION</b>	<b>MINOR CONCERN</b>	<b>MODERATE CONCERN</b>	<b>MAJOR CONCERN</b>
		maintenance activities.	configuration management and maintenance plan documents.
Verification and Validation Documentation	Software functional test plan, pass / fail criteria, and results.	Description of V&V activities at the unit, integration, and system level. System level test protocol, including pass/fail criteria, and tests results.	Description of V&V activities at the unit, integration, and system level. Unit, integration and system level test protocols, including pass/fail criteria, test report, summary, and tests results.
Revision Level History	Revision history log, including release version number and date.		
Unresolved Anomalies (Bugs or Defects)	No documentation is necessary in the submission.	List of remaining software anomalies, annotated with an explanation of the impact on safety or effectiveness, including operator usage and human factors.	

Figure 5.4: “Required documentation based on level of concern” Food and Drug Administration (2005).

### **Risk management**

The document “*Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices*” suggests proper risk management. The FDA considers whether the risk management is based on a consensus standard such as ISO 14971. The last review on this norm is from 2007, and the International Organization for Standardization (ISO) provides the following description. “The ISO 14971:2007 specifies a process for a manufacturer to identify the hazards associated with medical devices to estimate and evaluate the associated risks, to control these risks, and to monitor the

effectiveness of the controls. The requirements of ISO 14971:2007 are applicable to all stages of the life-cycle of a medical device” International Organization for Standardization (2007).

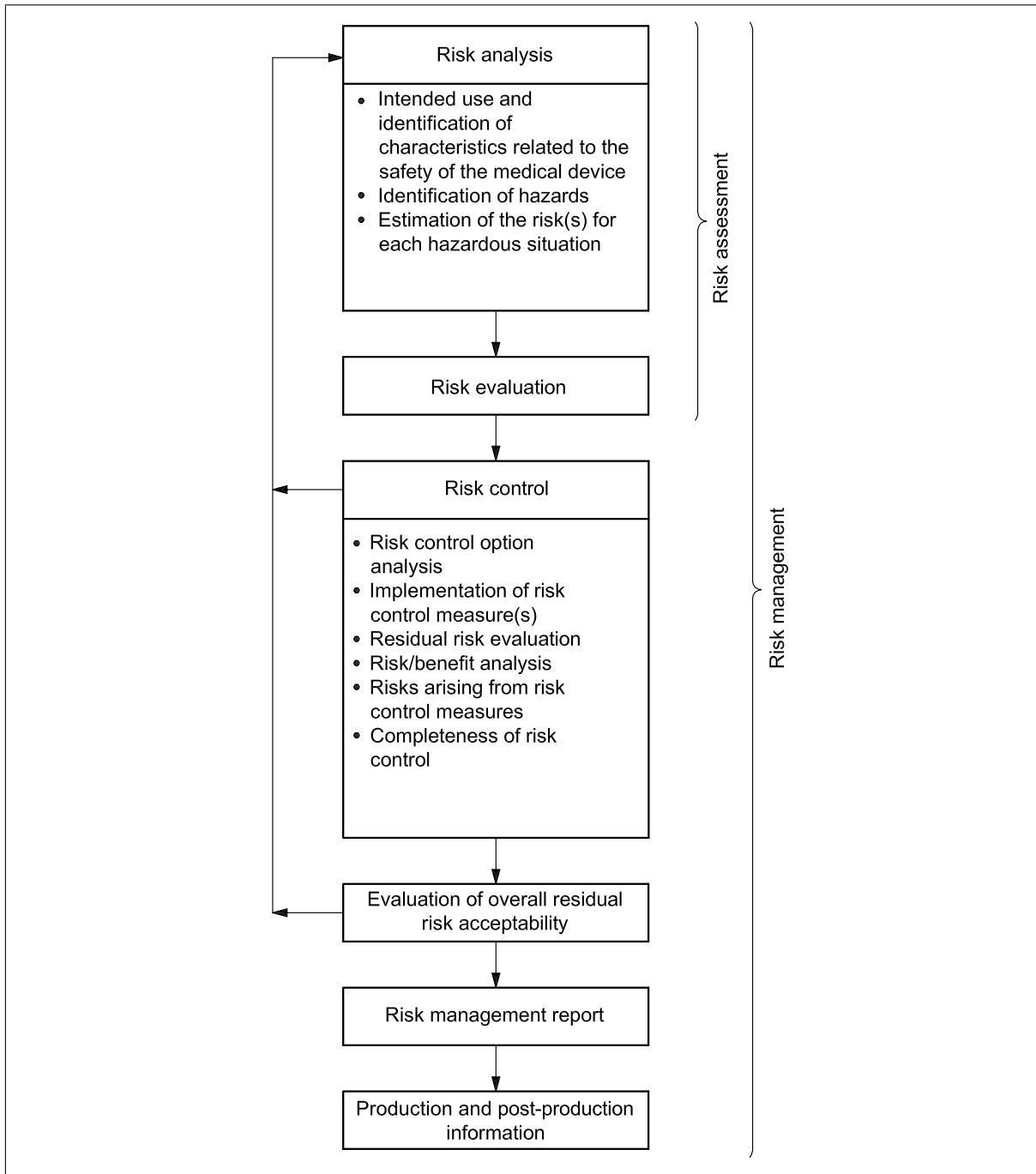


Figure 5.5: Risk management. “A schematic representation of the risk management process” British Standards Institute Staff, British Standards Institution and International Organization for Standardization (2009).

Risk management is an extensive topic, and we only present the risk management process graphically in this work to provide an overview. For more detailed information, we refer to specialist literature, such as the ISO 14971:2007 norm, and the Figure 5.5

is cited from this standard.

**Quality system regulation** The FDA has published regulations that address Quality system regulations that concern all manufacturers of medical devices. Part 820 of the FDA regulation deals with Quality system regulations, and is also known as current good manufacturing practice (CGMP). The regulations are only legal for device manufacturers who sell a finished device. Paragraph 820.30(l) defines the term “finished device” as: “Finished device means any device or accessory to any device that is suitable for use or capable of functioning, whether or not it is packaged, labeled, or sterilized.” Every manufacturer must hold a quality system manual, and hence established medical device producers already have one, and the quality system manual should include the design control process. The design input and output are two important elements in the design control process, and the manufacturer has to comprise them. The depth of the quality system implementation is up to the manufacturer, but the quality system manual should disclose how the company reaches its quality goals. Therefore, the goals should be described for the design and building phase, and the goals for quality control at the end of production should be specified in the manual. It is important to note that the quality system should be well documented in case the FDA audits the manufacturer. The conclusion for research departments like the Wadsworth Center is that it is compulsory for them to develop a quality system manual if they sell a medical device. Also, if they intend to develop and test prototypes, and the device itself is manufactured by someone else, a quality system manual is required for them. Therefore, the next paragraph deals with software validation, which includes design control process.

### **General Principles of Software Validation**

This guidance is valid for almost every software package used in the context with a medical device. The guidance documents also address stand-alone software that is considered a medical device. Software validation is part of Design control, which is a part of Quality system regulation. In other words, “TITLE 21 of FOOD AND DRUGS; CHAPTER I-PART 820 QUALITY SYSTEM REGULATION” says that: “each manufacturer shall establish and maintain a quality system that is appropriate for the specific medical device(s) designed or manufactured, and that meets the requirements of this part” Food and Drug Administration (2009b). The subpart C “Design Controls” includes under 820(g) “Design validation”, which every manufacturer shall establish, and the next paragraph explains this topic in more detail.

The guideline aims to support the requirements for software validation system. Soft-



ware validation is an important part of guidance "Software in the context of medical device" in Section 5.2.3, and hence the document contains itemization of the acceptable elements for the validation of software. "Planning, verification, testing traceability, configuration management and many other aspects of good software engineering discussed in this guidance are important activities that together help to support a final conclusion that software is validated" Food and Drug Administration (2002).

**Design control** After the concept phase, the product development process reaches the design control phase, and therefore the ideas resulting from the concept phase must be documented and formalized to form a safe product. This process is called design control and should take place after the concept was developed and before clinical trials are starting. The FDA published the manual "*Design Control Guidance For Medical Device Manufacturers*" in 1997 and the following paragraph gives an overview of the guidance. The figure 5.6 depicts the design control process, which consists of two closed loop processes.

1. Verification loop: design input → design process → design output
2. Validation loop: user needs → verification loop → medical device

Design control forms a controlled method to key out the product requirements and inputs. These input parameters are converted into engineering language by using the product specifications, and these specifications are transformed into prototypes and or implementations. The design outputs of the software are created either from the prototypes or implementations, and the inputs and outputs are linked up in a loop structure. The Figure 5.6 depicts this closed loop system, which contains design input, design output and verification.

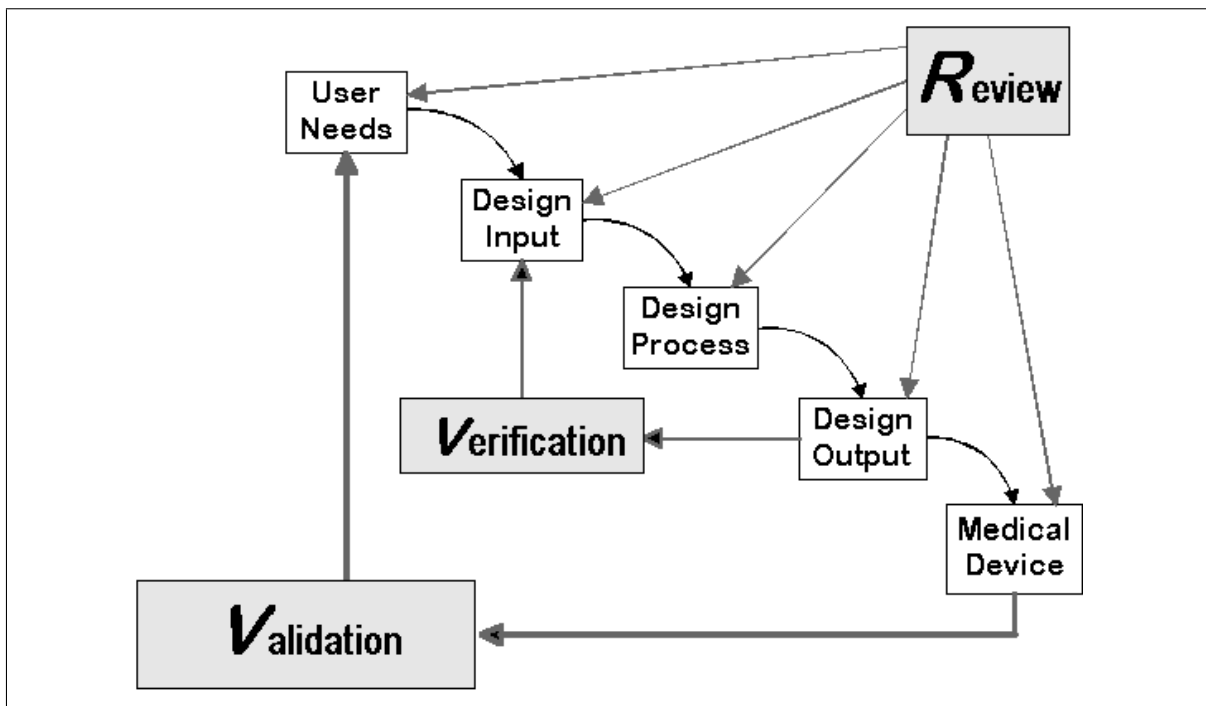


Figure 5.6: Design Control. “The figure illustrates the influence of design controls on a design process, which is an example for a traditional waterfall model” Food and Drug Administration (2009b).

The documentation of these reviews in the product development process are fundamental and mandatory for the manufacturer. The verification process ensures that the suitability of the design satisfied the needs of the health care personnel and patients. The FDA requires reporting of the iterative steps, and the validation must include a complete testing series that shows that the specifications and requirements matches each other. The next step after verification is software validation, which assures that the prototype meets the requirements of the user needs. Hence, the term validation is used for testing trials performed with a prototype to evaluate whether the prototype matches the user needs. Therefore, the validation should involve the target user and simulate the environment normally used. When the software validation is finished, the design can be transferred to manufacturing phase. This step also needs ongoing reviews and documentation.

### 5.3 Sequence of action

This section addresses the guidance documents and regulations regarding both diagnostic test SIGFRIED and EEG LI test. In particular, we define three classifications for each development result.

1. Medical device class
2. Predicate devices (“substantially equivalent”)
3. Level of concern

In our case, we already use an FDA approved device for signal acquisition, but two clinical diagnostic tests involve new signal processing software. Both development results use FDA approved signal acquisition devices that consist of hardware and software; hence, there are two possible ways to obtain an FDA approval for both clinical diagnostic tests.

Scenario I to cooperate with a signal processing device manufacturer and sell the development result as an upgrade of the existing software operating system.

Scenario II to sell the development result as stand alone software.

Both cases need an FDA approval certificate. As described earlier, a class I and II medical device is qualified for the 510k application process. First, we will determine the class of each innovation and then we will look for a “substantially equivalent” device on the market (predicate devices). The level of concern is the last topic, which is discussed for each research outcome.

**FDA approval requirements for EEG LI test** As the title suggests, this development result is based on the Electroencephalograph (EEG) (see Section 2.1.1, which is available in many hospitals and through private physicians. EEG recording has been well known for many years, and there are already several EEG-based devices on the market. Also, the FDA developed part 882.1400 exclusively for EEG, and thus the development result fits into this part, which is displayed in Figure 5.7.

TITLE 21--FOOD AND DRUGS  
CHAPTER I--FOOD AND DRUG ADMINISTRATION  
DEPARTMENT OF HEALTH AND HUMAN SERVICES  
SUBCHAPTER H--MEDICAL DEVICES

PART 882 -- NEUROLOGICAL DEVICES

Subpart B--Neurological Diagnostic Devices

Sec. 882.1400 Electroencephalograph.

(a) *Identification.* An electroencephalograph is a device used to measure and record the electrical activity of the patient's brain obtained by placing two or more electrodes on the head.

(b) *Classification.* Class II (performance standards).

Figure 5.7: Medical device class of electroencephalograph. Electroencephalograph is categorized as class 2 medical device.

We know now that EEG LI test is most likely considered a class II medical device, and the next step is to look for “substantially equivalent” devices. The FDA provides the “510(k) premarket notification database” online (<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm>) and there are two search options available, advanced and simple. The outcome of a search is a list with all premarket notifications that match the keywords, and the list consists of four columns. The last column includes a link to the summary or statement of the 510(k), which is typically a separate PDF file. The summary or statement always contains the paragraph “indications for use” and this description should be “substantially equivalent” to the research outcome. For the scenario I, we need to find a relevant 510(k) description of a signal acquisition device. The data which supported the development of EEG LI test is recorded with a signal acquisition device from the company g.tec Guger Technologies OG. The BCI lab at the Wadsworth has a strong relationship with this company through many years of collaboration. Hence, the lab has a solid foundation to cooperate with g.tec to launch this diagnostic test on the market. The figure 5.8 shows the intended use of the signal acquisition device g.USBamp, and the description of the intended use opens up the possibility of including the EEG LI test as an additional feature to the existing software of the device. The regulations listed in section 5.2.2 require a submission of a premarket notification in that specific case.

510(k) Number (if known): K060803

Device Name: g.USBamp

Indications For Use:

Measuring, recording and analysis of electrical activity of the brain and/or through the attachment of multiple electrodes at various locations to aid in monitoring and diagnosis as routinely found in clinical settings for EEG.

Figure 5.8: K060803. 510k summary of the device g.USBamp produced by the company g.tec Guger Technologies OG.

In the scenario II, we plan to sell the development result as stand-alone software, and a predicate device is available at the “510(k) premarket notification database”. The software is sold under the name “Nihon Kohden QP-160 AK EEG Trend Program” (see Figure 5.9 on page 82, but the indication of use prohibits any diagnostic conclusion.

510(k) Number (if known): K092573

Device Name: Nihon Kohden QP-160AK EEG Trend Program

Indications for Use:

The QP-160AK Trend program is a software-only device intended to be installed on the EEG-1200A series electroencephalograph to record, calculate, and display EEG data obtained from the EEG-1200A system. This device is intended to be used by qualified medical practitioners, trained in Electroencephalography, who will exercise professional judgment when using the information.

The intended use for each of the software's outputs is as follows:

- The EEG and aEEG waveforms are intended to help the user monitor the state of the brain.
- The user-defined Fast Fourier Transform (FFT) parameters of this software (FFT power) are intended to help the user analyze the EEG waveform.
- The burst suppression parameters of this software (interburst interval and bursts per minute) are intended to aid in the identification and characterization of areas of burst-suppression pattern in the EEG.

This device does not provide any diagnostic conclusion about the patient's condition to the user.

Figure 5.9: K092573. 510k summary of the device Nihon Kohden QP-160 AK EEG Trend Program.

The indication of use for the device g.usbamp includes the term diagnostic, but, in general, the term diagnostic has a huge impact on the level of concern (see 5.2.3). It is

clear that the diagnostic test does not have a major level of concern, but the distinction between moderate versus minor level of concern needs a closer explanation. EEG LI test aims to provide information for a medical doctor, and it is up to the doctor to what extent the information influences the diagnosis. We recommend that the application include a statement from a medical doctor that answers this question, and the inventor should decide carefully whether or not the indication of use includes a diagnostic purpose. The second question for determining the moderate level of concern deals whether the software accessorizes a moderate level of concern device. The innovation does not control any device function, and does not provide input information for any medical device. The outcome of the software is displayed on a third party monitor, so this question can be answered in the negative.

510(k) Number (if known): <u>          K002631          </u>
Device Name: <u>          eemagine EEG (Software)          </u>
Indications For Use:  The software is intended for use by a trained/qualified EEG technologist or physician on both adult and pediatric subjects for the visualization of human brain function by fusing a variety of EEG information with rendered images of an idealized head model and an idealized MRI image.

Figure 5.10: K002631. 510k summary of the device eemagine EEG software.

During our premarket notification database research, we found two additional 510ks that can support the submission for EEG LI test. They are presented in Figures 5.10 and 5.11.

510(k) Number: K090019

Device Name: Natus Neuroworks, Model 104196

**Indications for Use:**

The Neuroworks is EEG software that displays physiological signals. The intended user of this product is a qualified medical practitioner trained in Electroencephalography. This device is intended to be used by qualified medical practitioners who will exercise professional judgment in using the information.

- The Neuroworks EEG software allows acquisition, display, archive, review and analysis of physiological signals.
- The Seizure Detection component of Neuroworks is intended to mark previously acquired sections of the adult (greater than or equal to 18 years) EEG recordings that may correspond to electrographic seizures, in order to assist qualified clinical practitioners in the assessment of EEG traces. EEG recordings should be obtained with full scalp montage according to the standard 10/20 system.
- The Spike Detection component of Neuroworks is intended to mark previously acquired sections of the adult (greater than or equal to 18 years) EEG recordings that may correspond to electrographic spikes, in order to assist qualified clinical practitioners in the assessment of EEG traces. EEG recordings should be obtained with full scalp montage according to the standard 10/20 system.
- The aEEG functionality included in Neuroworks is intended to monitor the state of the brain. The automated event marking function of Neuroworks is not applicable to aEEG.
- Neuroworks also includes the display of a quantitative EEG plot, Compressed Spectrum Array (CSA), which is intended to help the user to monitor and analyze the EEG waveform. The automated event marking function of Neuroworks is not applicable to CSA.

This device does not provide any diagnostic conclusion about the patient's condition to the user.

Figure 5.11: K991054. 510k summary of the device Natus Neuroworks, Model 104196.

**FDA approval requirements for SIGFRIED** The novel functional brain mapping technology SIGFRIED uses data recorded from an implanted electrode, and the implantation procedure is exclusively performed in a hospital environment. The signal acquisition process (see Figure 2.2 on page 10) consists of two class II medical devices. The first device is the aforementioned data amplifier g.USBamp (see Figure 5.8 on page 82), and the second is the implanted cortical electrode used to record data from the cortex. For the first recordings, we used subdural electrodes from the company Ad-tech, and the 510k of these devices is depicted in Figure 5.12 on page 85.

510(k) Number (if known): \_\_\_\_\_

Device Name: Subdural Electrodes

Indications for Use:

The AD-TECH Subdural Electrodes (Dual-Sided Interhemispheric, Grid, Intraoperative, Strip, Wyler) are intended for temporary (< 30 days) use with recording, monitoring and stimulation equipment for the recording, monitoring and stimulation of electrical signals on the surface of the brain. The recording of electrical activity supports definition of the location of epileptogenic foci and brain mapping.

Figure 5.12: K053363. 510k summary of the device subdural electrodes.

The FDA created the section 882.1310 for cortical electrodes which categorizes a cortical electrode as a class II device and the Figure 5.13 on page 85 illustrates this section.

TITLE 21--FOOD AND DRUGS  
CHAPTER I--FOOD AND DRUG ADMINISTRATION  
DEPARTMENT OF HEALTH AND HUMAN SERVICES  
SUBCHAPTER H--MEDICAL DEVICES

PART 882 -- NEUROLOGICAL DEVICES

Subpart B--Neurological Diagnostic Devices

Sec. 882.1310 Cortical electrode.

(a) *Identification.* A cortical electrode is an electrode which is temporarily placed on the surface of the brain for stimulating the brain or recording the brain's electrical activity.

(b) *Classification.* Class II (performance standards).

Figure 5.13: Medical device class of cortical electrode. Cortical electrode is categorized as class 2 medical device.

The last paragraph verifies that there are only class II used in combination with SIGFRIED. The innovative functional brain mapping technique SIGFRIED contains signal processing software, like the already described EEG LI test. There are no differences evident in the content of the classification of the medical device between these two diagnostic tests, so SIGFRIED is eligible for the category medical device class II. The next important classification for software in content with a medical device is the "level of concern"(see 5.2.3), so we explain the usage of the software more precisely. Currently, SIGFRIED is used as a pre-detection of brain functions and the result of



the pre-detection supports the sequence of the Electrocortical stimulation(see Section 2.2.1. In other words, SIGFRIED is not used for diagnosis, and no conclusions about the patient's conditions are based on the outcome of SIGFRIED. The outputs of "Sigfried" are colored figures of brain function, which are displayed on a third party monitor, and the innovation does not support information for any device. These facts indicate that SIGFRIED can be categorized as Minor level of concern.

The last step is to assess whether the research outcome is authorized for the pre-market notification (see Section 5.2.2). Therefore, the key element is to show that the innovation is not considered a novel technology by the FDA, because then the inventor must go through the more complex pre-marketing approval process or through the "Evaluation of automatic class III designation provision" process. The best way to verify that the development result is not a novel technique is to find matching predicate approved medical devices. Every named predicate device for the EEG LI test is applicable for SIGFRIED too. In particular, the indication of use for the device eemagine EEG software (see Figure 5.10 on page 83) sounds qualified as a predicate device.

510(k) Number (if known): <u>K050833</u>
Device Name: <u>Electrode Junction Box, JE-921A series</u>
Indications For Use:
<p>The device is intended to acquire, store, and transfer biophysical parameters to EEG machines for the purpose of assisting the diagnosis of neurological and sleep disorders, measurement and display of cerebral and extracerebral activity for EEG and Sleep Studies. These data, may be used by the clinician in Sleep Disorders, Epilepsies and other related disorders as a diagnostic tool. As with the predicate, the information transferred to EEG will be stored, interpreted and printed with commercially software programs available with Nihon Kohden marketed products.</p> <p>The device is intended for use by medical personnel in any location within a medical facility, physician's office, laboratory, clinic or nursing home or outside of a medical facility under supervision of a medical professional. The device will be available on all patient populations, including pediatrics.</p>

Figure 5.14: K050833. 510k summary of the device Electrode Junction Box, JE-921 A serie.

We also note the 510k of the device Electrode Junction Box (see Figure 5.14) to provide a complete overview of all relevant predicated devices for the research outcome SIGFRIED.

**Time line and cost estimation** The table 5.1 list all task to prepare a FDA approval application and DI Brunner, software engineer at the Wadsworth center estimated the required times to accomplish the tasks.

Task	EEG LI test	SIGFRIED
Overhaul the GUI	0.30	0.25
Level of Concern	0.30	0.20
Software Description	0.10	0.10
Device Hazard Analysis	0.15	0.30
Software Requirements Specification	0.20	0.20
Traceability Analysis	0.15	0.15
Verification and Validation Documentation	0.35	0.35
Revision Level History	0.10	0.10
Total effort to prepare diagnostic tests's SW for the FDA approval	<b>1.65</b>	<b>1.65</b>

All number have the unit: [years/employee]

Table 5.1: Software development effort estimation. The Table estimates the development effort to prepare the software SIGFRIED and EEG LI test for the Food and Drug Administration approval application. The numbers represent Person Years required from software engineers.

For both development results 1.65 Person Years are necessary to prepare the Pre-market notification application.

The next citation shows the duration time of a Premarket notification application. "FDA's fiscal year 2009 goal is to review and decide on 90 percent of 510(k) submissions within 90 days and 98 percent of them within 150 days. The comparable goals for a Premarket Approval Application (PMA) is to review and decide upon 60 percent of original PMA submission in 180 days and 90 percent of them within 295 days" Crosse (2009). 180 day equal 0.25 years thus the total time effort for the FDA approval is 1.9 Person years.

The table 5.2 shows the total mount of money, that the Wadsworth center spends to employ a software engineer with the grade P25. The specification for a p25 grade software engineer are a Master degree and several years of experience.

Software engineer				
Base Salary	Fringe rate	Fringe cost	Indirect cost	Total
90,844	37.50%	34,067	85,064	209,975

Table 5.2: Software engineer salary. All numbers have the unit USD per year.

The required time multiplied by the salary equals the total personal cost of the

certification.

$$\$209,975 * 1.9 = \$398,953$$

“For the applicant, the standard fee provided to FDA at the time of submission is also significantly lower for a 510(k) submission than for a PMA submission. In fiscal year 2009, for example, the standard fee for 510(k) submissions is \$3,693 while the standard fee for original PMA submissions is \$200,725” Crosse (2009).

$$\$398,953 + \$3,693 = \$402,646$$

The last equation sums the personal cost and the applications fee that are the total expenses for the certification of one clinical diagnostic test.

## **5.4 Summary of regulatory environment**

For commercialization, every medical device must be approved by the Food and Drug Administration. The FDA categories the medical device into class, which decide the volume of certification process. However, both clinical diagnostic tests are considered as class two medical device and they are qualified for a Premarket Notification (510k) application, which is based on a predicate device. This chapter list suitable predicate devices for both development results.

For devices that contain software, the FDA requires additional documentation and the volume is based on the level of concern, which is independent of the medical device class. For both development results, the classification in either minor or moderate level of concern is unclear. If these tests are performed in addition to the established methods than minor concern is reasonable. If these tests replace the established methods than moderate level of concern is suitable, which required more documentation and detailed safety tests.

In conclusion, the FDA guidelines are precise thus the whole application process and required documentation are clear and transparent for both tests. The total cost for the certification of one test are \$402,646.

## **6 Reimbursement policy of a medical device in US**

Chapter 4 evaluated the market demand, particularly the available market of each development result. Chapter 5 explained all necessary milestones to gain market clearance for a medical device which allows the manufacturer to commercially distribute the device within a US market. This chapter deals with the reimbursement policies of the US medicare companies, which cover the treatment costs of their clients and the chapter's aim is to clarify whether it is possible to obtain reimbursement of the development results. Furthermore, this chapter talk about the Medicare coverage determination in general. The final chapter of this thesis discusses the purchasing process between manufacturer and hospital, which is the overall goal of the manufacturer.

The chapter market of development results explained the singularity of the health care field, which basically means that the payer for the treatment expenses is typically not the patient. Instead, a private or government-run insurance plan reimburses the hospital or physician for the performed medical, surgical, and diagnostic services. Hence, the success of an innovation in the medical device field depends heavily on whether the insurance companies cover the treatment that is performed with the recently developed medical device. There is a large time and cost-saving potential if the manufacturer considers this aspect early in the innovation process. Hence, the inventor should be aware of relevant coverage regulations during the development phase of an novel medical device so that the design of the development result meets the reimbursement policy. Also, the documentation of each design step and trial should match the coverage requirements in the first place to ensure a fast and cost-effective innovation process.

This chapter highlights the important factors for the medicare coverage decision in the United States. In particular, we address the coverage conditions of Center of Medicare and Medicaid Services, which is the nation's largest health insurance program, as explained in Section 6.1. The Section 6.2 outlines the three different reimbursement codes e.g., International Statistical Classification of Diseases 9th rev. and Current Procedural Terminology. The Section 6.2.2 focuses on the Current Procedural Terminology

codes, because this reimbursement code is adequate for SIGFRIED and EEG LI test. In the reimbursement field, the three major objectives for an innovative medical device, which are essential for the overall success of research outcome, are:

1. Positive coverage decision
2. Assigned reimbursement code
3. Adequate amount that can be reimbursed

At first glance, these goals may give the impression that reimbursement coverage is simple and straightforward. In reality, it is a complex and time-consuming undertaking. Gregory Raab states these reimbursement challenges very well in the paper *“From Medical Invention to Clinical Practice: The Reimbursement Challenge Facing New Device Procedures and Technology-Part 1: Issues in Medical Device Assessment”*, and the following paragraph is cited from this article.

“Insurer coverage and payment processes not only determine whether current technologies will be made available to patients; they also create a climate that can provide incentives or disincentives for manufacturers to innovate in the first place. This was documented in a 2000 a medical device industry study conducted by the Lewin Group, which was based on a survey of device manufacturers in the United States, an analysis of secondary research information, and confidential interviews with industry executives, security analysts, and other informed observers. The Lewin survey identified Medicare coverage and payment processes as often being “inconsistent and confusing” and noted that, although manufacturers express similar views about private health insurer coverage and payment processes, “concerns regarding Medicare are particularly acute, reflecting the program’s size and scope, as well as the program’s influence on payment policy in all sectors of the health care market”.

In examining Medicare’s coding, coverage, and payment processes, the Lewin Group’s study found that the systems for making these decisions are “separate and largely uncoordinated”; manufacturers are required to negotiate “multiple, distinct, and complex processes”. As a result, Lewin found that it can take the Centers for Medicare & Medicaid Services officials from 15 months to 5 years to add new medical technologies to the Medicare program. The time it takes manufacturers to manage these reimbursement hurdles is particularly troublesome because most medical devices have life spans of only 12 to 18 months. Most device manufacturers surveyed by Lewin felt that the Medicare coverage and payment processes were not clear, transparent, predictable, or consistently and fairly applied” Raab and Parr (2006a).

## 6.1 Center of Medicare & Medicaid Services

The Center of Medicare & Medicaid Services (CMS) plays a major role in the medicare coverage process because it administers the medicare program of the US. The CMS is part of the Department of Health and Human Services and is considered a federal agency. TITLE XVIII-HEALTH INSURANCE FOR THE AGED AND DISABLED set up the legal basis for the medicare program, which is the nation's largest health insurance program covering approximately 41 million Americans. "Beneficiaries consist primarily of individuals 65 years of age or older, some disabled people under 65 years of age, and people with end-stage renal disease (permanent kidney failure treated with dialysis or a transplant)" Department of Health and Human Services (2003a).

The Center of Medicare and Medicaid Services established a coverage decision process for devices and treatments. However, the private insurers normally follow the coverage decisions of the CMS. The Center of Medicare and Medicaid Services distinguishes between two coverage determinations.

1. Local coverage determination (LCD)
2. National coverage determination (NCD)

The local coverage determinations are decided by local contracts, and the vast majority of determinations are LCD. "Currently, there are in total 6000 LCDs established, but nationwide, only approximately 300 NCDs are installed" Schoonmaker, Bagley and Scanlan (2002). Especially for a new device, it is common to apply first for local coverage determination and then consider pursuing an NCD in the future. First, we describe generally valid aspects for both coverage decisions, then we explain each in detail.

**Coverage criteria and requirements** In the beginning of this paragraph, the different interests of the FDA and CMS are explained and afterwards, the coverage criteria and requirements for a BCI-based medical device are discussed. The FDA approval process verifies that a service or device is safe and effective, but it does not check whether there is a more efficient device or service on the market. Generally the CMS accepts only a request for a device that is FDA approved. In other words, a medical device must have one of these FDA approvals as a basic prerequisite for a coverage determination:

- Premarket approval (see Section 5.2.1)
- Premarket Notification 510(k) (see Section 5.2.2)
- Category B IDE devices (see Section 5.1)

- Hospital Institutional Review Board (IRB) approved IDE devices (see Section 5.1)

Unfortunately, the Category A IDE devices are excluded from the coverage decision, as FDA explains on their Web site, <http://www.fda.gov>. The relevant parts of the exclusion are summarized in the next paragraph.

“The Medicare program has historically interpreted the statutory terms “reasonable and necessary” to mean that a service or medical device must be safe and effective, medically necessary and appropriate, and not experimental in order to qualify for reimbursement. For Medicare coverage purposes, the term “experimental” has been used synonymously with the term “investigational.” Therefore, with rare exceptions, an FDA-approved Investigational Device Exemption (IDE) application served as an indication that the device was not “reasonable and necessary” within the meaning of the Medicare program. Thus, Medicare coverage was denied for devices which were under an IDE and had not yet received premarket notification clearance and or premarket approval. There was increasing recognition, however, that there are devices that are refinements of existing technologies or replications of existing technologies made by other manufacturers. Many of these devices are under an FDA-approved IDE as a means of gathering the scientific information needed for the FDA to establish the safety and effectiveness of that particular device, even though there is evidence that the device type can be safe and effective. Such devices could be viewed as “reasonable and necessary” by Medicare and thus be reimbursed if it were possible to identify these devices to Health Care Financing Administration” cf. American Medical Association (1995). Therefore the FDA categorizes IDE certifications into two classes, and only a IDE Category B device can be reimbursed:

- IDE Category A - Experimental
- IDE Category B - Investigational; Non-experimental

**What means “reasonable and necessary”?** The Medicare program aims to reimburse the most efficient treatment, and therefore the CMS bases their decision on “What is reasonable and necessary” over the last 35 years Department of Health and Human Services (2003b). However, the CMS made several attempts to describe “reasonable and necessary” more precisely, but they could not agree on one definition. “Medicare officials tried to include “cost-effectiveness” and “added value” as coverage criteria in formal regulations governing the Medicare coverage review process. These regulatory attempts were controversial, because manufacturers and medical groups strongly objected to introducing cost considerations into coverage decision making. As a result, neither of these regulations was finalized, and the CMS has decided to forgo

overt efforts to add economic consideration to nation coverage decision making. Nevertheless, it is generally acknowledged by CMS staff members that economic and cost considerations are factors considered in evaluation new technologies and that they are an implicit, if not an explicit, factor in the decision-making process itself” Raab and Parr (2006a). Which devices are covered by the Medicare program?

G.Gregory Raab answered the question with the following statement: “To be covered by Medicare, new medical procedures and technologies must fit within a benefit category set out in the Medicare statute and be found to be “reasonable and necessary” for the diagnosis or treatment of illness or injury” Raab and Parr (2006b). As mentioned earlier, the CMS does not provide a precise description of the term “reasonable and necessary”, but the CMS published a list of services and devices that are not covered by them. This list was released as 42 Code of Federal Regulations (CFR) 411.15 in 2004, and the next list outlines the relevant exclusions for the field BCI:

1. Routine physical checkups such as:
  - (a) performed for a purpose other than treatment and diagnosis
  - (b) required by insurance companies or government agencies.
2. Personal comfort service, except as necessary for the palliation or management of terminal illness.
3. Any services that are not reasonable and necessary for following purpose
  - (a) For the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member.
  - (b) In the case of hospice services, for the palliation or management of terminal illness.
4. Experimental or investigational devices, except for certain devices-
  - (a) Categorized by the FDA as a nonexperimental/investigational (Category B) device
  - (b) Furnished in accordance with the FDA-approved protocols governing clinical trials.
5. Services furnished to SNF residents: Any physical, occupational, or speech-language therapy services, regardless of whether the services are furnished by (or under the supervision of) a physician or other health care professional, and regardless of whether the resident who receives the services is in a covered Part A stay.



Maintained by the CMS, the Medicare Coverage Database (MCD) contains all Local Medical Review Policies (LMRPs), Local and National Coverage Determinations. The CMS's Web site, <http://www.cms.gov/mcd/search.asp?from2=search.asp&>, provides access to this database, which is the official source of all local payment policies around the US. The Medicare Coverage Database also contains all local medicare contractors that follow the Local Coverage Determinations and Local Medical Review Policies.

**Published study** In general, published studies have a large impact on the coverage determination. The CMS and also the local medicare companies review the relevant published papers and the conclusion of the papers are considered in the decision. Hence published papers support the coverage application and the Figure 6.1 depicts hierarchy of the paper's impact.

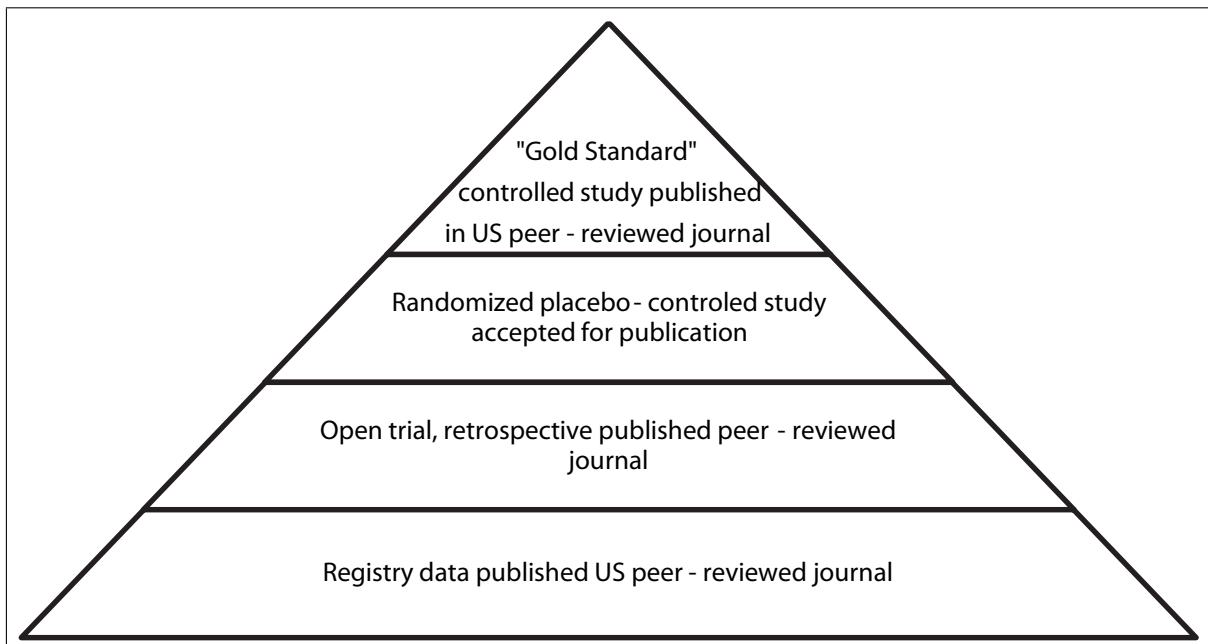


Figure 6.1: Hierarchy of papers. This figure displays the impact factor of published studies in the medicare coverage determination.

The gold Standard are controlled study published in US peer-reviewed journals and the coverage determination statement form the insurance companies contain a list of references, which shows that papers

### 6.1.1 Local coverage determination

According to the CMS, a Local coverage determination is defined as: "Local coverage determination (LCD) means a decision by a fiscal intermediary or a carrier under Medicare Part A or Part B, as applicable, whether to cover a particular service on an

intermediary-wide or carrier-wide basis in accordance with section 1862(a)(1)(A) of the Act. An LCD may provide that a service is not reasonable and necessary for certain diagnoses and/ or for certain diagnosis codes. An LCD does not include a determination of which procedure code, if any, is assigned to a service or a determination with respect to the amount of payment to be made for the service” Department of Health and Human Services (2003a). Medicare Part A, B and C are also defined by the CMS, but the Medicare program reimburses only treatments that are contained in Part A or B.

**Part A:**“The hospital insurance program covers certain care provided to inpatients in hospitals, critical access hospitals, skilled nursing facilities, as well as hospice care and some home health care” cf. Department of Health and Human Services (2003a).

**Part B:**“The supplementary medical insurance program covers certain physicians’ services, outpatient hospital care, and other medical services that are not covered under Part A” cf. Department of Health and Human Services (2003a).

**Part C:**“Known as the Medicare+Choice (M+C) program, this provides beneficiaries with various options, including the right to choose a Medicare managed care plan or a Medicare private fee-for-service plan. Under the M+C program, an individual is entitled to those items and services (other than hospice care) for which benefits are available under Part A and Part B. An M+C plan may provide additional health care items and services that are not covered under the original Medicare program” cf. Department of Health and Human Services (2003a).

“CMS has delegated authority to Medicare contractors to develop and issue contractor-specific policy that identify the circumstances under which particular items or services will be covered in a geographic area. Medicare contractors typically have developed policies in the form of local medical review policies (LMRPs), which include four different types of provisions-coding, benefit category, statutory exclusions, and medical necessity provisions (i.e., those provisions interpreting the reasonable and necessary provision of the Medicare statute)” Scherb and Kurlander (2006)

### **6.1.2 National coverage determination**

National Coverage Determination is a long-lasting application process, and uncommon for a new technology or device. Hence, the usual route for a new device is to apply for a Local Coverage Determination and subsequently for a National Coverage Determination. This paragraph explains only the basics of the NCD process, because a manufacturer normally does not consider an NCD for an innovation.

The Center of Medicare and Medicaid Services formulated a guideline for the National Coverage Determination, and this guideline is modeled on the guidance documents

from the FDA. The Federal Register volume 68, number 187 published this document under the title: “Medicare Program; Revised Process for Making Medicare National Coverage Determinations” in 2003, and the purpose of this document is to outline the NCD process. Hence these documents contain information that is relevant for the diagnostic tests, including a definition of the term National Coverage Determination: “(NCD) means a decision that CMS makes regarding whether to cover a particular service nationally under title XVIII of the Act. An NCD does not include a determination of what code, if any, is assigned to a service or a determination with respect to the amount of payment to be made for the service ” Department of Health and Human Services (2003a). Next, we describe the necessary components of an NCD submission. The application must be submitted in written and electronic form, and it must be declared as “formal request for an NCD”. Furthermore, the submission must include a statement from the requestor that explains which benefit category of the Medicare program is appropriate for the device. In addition, there are several required documents, displayed in the next list based on Department of Health and Human Services (2003b):

1. Detailed description of the treatment or device
2. Estimation of the target Medicare population and explanation of the considered population
3. Any information regarding the medical benefit of the treatment or device
4. Explanation of whether the device is operated by a physician or patient, and details of the procedures that involve the device (design, purpose and method)
5. A statement from the requestor (in cases in which there is an aggrieved party, the statement must be from that party) containing the following:
  - (a) An explanation of the relevance of the evidence selected
  - (b) Rationale for how the evidence selected demonstrates the medical benefits for the target Medicare population
  - (c) Information that examines the magnitude of the medical benefit
  - (d) Reasoning for how coverage of the item or service will help improve the medical benefit to the target population
  - (e) In the case of an aggrieved party, how that party is “in need” of the item or service.
6. A description of any clinical trials or studies currently underway that might be relevant to a decision regarding coverage of the item or service

7. Information involving the use of a drug or device subject to FDA regulation as well as the status of current FDA regulatory review of the drug or device involved. An FDA regulated article would include the labeling submitted to the FDA or approved by the FDA for that article, together with an indication of whether the article for which a review is being requested is covered under the labeled indication(s)
8. In the case of items that are eligible for a 510(k) clearance by the FDA, identification of the predicate device to which the item is claimed to be substantially equivalent.

However, a positive NCD was issued for the awake craniotomy, which implants an electrode grid in the patient's brain, followed by extended monitoring to diagnose resectable seizure foci. The statement's title is "Stereoetaxic Depth Electrode Implantation", and the Figure 6.2 displays the statement.

**160.5 - Stereoetaxic Depth Electrode Implantation**  
**(Rev. 1, 10-03-03)**  
**CIM 50-40**

Stereotaxic depth electrode implantation prior to surgical treatment of focal epilepsy for patients who are unresponsive to anticonvulsant medications has been found both safe and effective for diagnosing resectable seizure foci that may go undetected by conventional scalp electroencephalographs (EEGs).

The procedure employs thin wire electrodes which are implanted in the brain of the focal epileptic patient for EEG monitoring. By taking several readings during seizure activity, the location of the epileptic focus may be found, so that better informed decisions can be made regarding the surgical treatment of persons with intractable seizures.

Figure 6.2: Medicare national coverage determination. "The document *Medicare National Coverage Determinations Manual Chapter 1, Part 2 (Sections 90 - 160.26) Coverage Determinations* includes the coverage determinations dealing with electrocortical stimulation. Hence, this document contains also the statement about electrocortical stimulation for the purpose of functional brain mapping in content of epilepsy surgery" cf. Center of Medicare & Medicaid Services (2010).

As mentioned in the Section 2.2.1 electrocortical stimulation is well established around the USA, so the CMS decided to cover this treatment. The document also includes decisions about the use of electrocortical stimulation for another purpose: functional brain mapping. For example, "Treatment of Motor Function Disorders with Electric Nerve Stimulation" is not covered by the CMS, and this statement and other relevant statements can be found in the appendix.

### 6.1.3 Sequence of action

Our plan to seek reimbursement is as follows. Notably, no further technical development or preparatory research is needed. Hence, our first step is to get our two development results classified as IDE Category B devices, and then seek approval for an approved clinical trial. We will also need to demonstrate that the procedure does not cost more than a conventional procedure, which is already demonstrated in the chapter 3. Next, we will approach local insurance companies to see if they will reimburse us for our clinical trials.

This plan is based partly on “*Medicare Benefit Policy Manual Chapter 14 - Medical Devices*”, which describes the items that may influence an insurer’s decision regarding reimbursement. This text is reviewed below, along with our approach to addressing each item.

For dates of service on or after November 1, 1995, Medicare may cover certain FDA-approved and Institutional Review Board (IRB) approved investigational devices and services, provided the investigational device meets certain conditions. The box below copies the text describing these conditions, followed by italicized text that describes how we will address them.

- “Appears on the listing of devices eligible for coverage/payment on CMS’ master file of IDE devices” Center of Medicare & Medicaid Services (2010). *We will ask the FDA to add our device to this list;*
- “Is reasonable and necessary for the individual patient” Center of Medicare & Medicaid Services (2010). *We have published articles that prove that our clinical diagnostic tests are reasonable and necessary. Determinations for individual patients will be made through practicing neurosurgeons who work with many potential patients, such as Dr. Ritaccio;*
- “The device or services associated with the use of a device were provided to the beneficiary within the start and end dates contained in the master file” Center of Medicare & Medicaid Services (2010). *We will be responsible for ensuring that our work is conducted within the appropriate time span*
- “There is no national coverage policy that would otherwise prohibit Medicare coverage” Center of Medicare & Medicaid Services (2010). *We have already explored this question, but will reconfirm it as needed.*

However, the preceding list only describes conditions that must be met before Medicare may cover relevant expenses. That is, insurers are not required to cover costs

relating to any device or study that meets those conditions. The same document then lists criteria that “must also be applied when making coverage determinations on FDA-approved IDE Category B devices.” This list is reproduced here, along with italicized text that we added:

- The device must be used within the context of the FDA-approved clinical trial. *We will seek this FDA approval;*
- The device must be used according to the clinical trial’s approved patient protocols. *We will develop and heed appropriate protocols, drawing on our extensive experience with clinically oriented research;*
- There may be an established national policy as contained in existing manual instructions, e.g., National Coverage Determinations Manual instructions, etc. *We noted existing tests above, but there is nothing unique to our work;*
- In the absence of national policy, there may be a local policy for similar FDA-approved devices. *We are not aware of any such local policies, but will check again as needed;*
- There may be Policy/Position papers or recommendations made by pertinent national and/or local specialty societies. *We are not aware of any such national or local societies that would issue relevant policies, but will check again as needed. Indeed, there has been some discussion of forming a BCI Society that could establish relevant policies, and we are in contact with the organizers. ”*

As noted, these criteria must be considered, but reimbursement still depends on local contractors’ decisions. This is addressed in the book “*Overview of Medicare Coverage of Clinical Trials*”: “Devices used pursuant to an FDA-approved IDE that are classified as Category B are eligible for full Medicare coverage. Unlike the limited Medicare coverage afforded by the routine costs policy, the Category B IDE policy authorizes Medicare coverage for the investigational item itself as well as for routine costs associated with the clinical trial. The investigational nature of Category B devices is neither sufficient reason to grant nor deny Medicare coverage. Such devices are covered only if they meet all other Medicare coverage requirements and coverage is not precluded by a national noncoverage policy. Although a Medicare contractor may deny coverage for several reasons, it cannot refuse to cover routine costs because of the investigational nature of the use of the device” cf. Becker and Whyte (2006)

### **6.1.4 Summary of the reimbursement coverage determination**

Because the market for an medical device in the BCI field is limited, it may not be suitable to apply for a NCD, which requires elaborate documents. For SIGFRIED, the NCD of the Stereotaxic Depth Electrode Implantation (see Figure 6.2 on page 97) ensures that physician will be reimbursed for the implantation of grid electrodes in epilepsy patients' brains. Thus, additional functional brain mapping with SIGFRIED takes little effort, and SIGFRIED's result can significantly improve the outcome of the epilepsy surgery.

Because the local insurance companies never developed a detailed and generally valid guideline that applies to all local insurance companies, it is very difficult to predict the outcome of a typical LCD and to be on top of the LCD procedure. Thus, for the two diagnostic tests, it is necessary to contact the local insurance companies to determine whether they would cover the tests.

## **6.2 Reimbursement code**

The last section discussed the medicare coverage process. Notably, a coverage decision does not determine the amount of reimbursal. The reimbursement code assigns the amount of money which can be reimbursed by a Medicare carrier, and thus the reimbursement code process has a large impact on the innovation process. For any innovation, a key goal is establishing an adequate amount of money that the hospital or physician receives for a treatment or diagnosis. "If a new procedure involves more costly equipment, is more difficult to perform, or requires more skill than current procedures, new codes are a necessary precondition for the new procedure's securing a higher payment rate. New codes also spur insurers to consider whether the new procedure should be covered and, if it is covered, to spell out whether the coverage is limited in terms of patient indications, sites of care, or qualified providers" Raab and Parr (2006a).

A standardized coding system should also ensure an effective and less bureaucratic reimbursement process between insurance companies and health care facilities and practitioners. In order to reach this goal, the reimbursement codes contain two essential features. First, the code can be processed in an online billing system, and hence the whole process can be done via computer. Second, the reimbursement code states precisely the treatment's procedure and the amount that can be reimbursed.

The American Medical Association (AMA) plays an important role in the reimbursement code process, because they are in charge of the Current Procedural Terminology CPT

codes, which are used in the whole country. In addition to the CPT codes, two other billing codes exist, and all of these codes are shown below.

1. Current Procedural Terminology CPT (identify physician procedure and payment for outpatient, laboratory and ambulatory surgical fees)
2. The International Statistical Classification of Diseases 9th rev (ICD-9) code (mainly for inpatient payment)
3. Healthcare Common Procedure Coding System (HCPCS) code set (mainly for Medicare physician fee and hospital outpatient prospective payment)

Before explaining each payment code system, we present a study that shows the timing of an application. “The coding decisions for ICD-9 codes, CPT codes, and HCPCS codes are generally made on an annual basis. The Lewin Group found that it takes a minimum of 15 months to secure a new code because of filing requirements. However, depending on the timing of the product launch, requirements associated with requesting a code, and the time required for new codes to become effective once decisions have been made, it may take as long as 27 months after a new technology has been cleared by the FDA for a new code to become effective” Raab and Parr (2006a). First, we address the ICD-9 code system, particularly the term “diagnosis related group (DRG)”. Second, we state the application process for a new CPT code, and we also provide a selection of CPT codes that are relevant for our development results.

### **6.2.1 International Statistical Classification of Diseases 9th rev code**

“Based on the World Health Organization disease classification system, the International Statistical Classification of Diseases 9th rev code (ICD-9-CM) are the official method of coding diagnoses and procedures associated with hospital utilization in the United States. ICD-9-CM codes, Volumes 1 and 2, are used to report a patient’s diagnosis or condition and are used by third-party payors to determine whether the service or product is warranted based on the patient’s diagnosis or symptoms. For Medicare billing purposes, ICD-9-CM Volume 3 codes classify hospital inpatient procedures. These codes are also included on Medicare claims and drive the payment methodology for acute care hospital inpatient services. The National Center for Health Statistics and CMS maintain and annually update the ICD-9-CM procedure codes.” Scherb and Kurlander (2006).



**Diagnosis-related group (DRG)** The DRG classification system is the most common system for categorizing urgent care inpatients and evaluating case mix. Case mix is an average of determining and evaluating the kind of patients a hospital treats. Diagnosis-related groups cases that are clinically the same and require identical resources. One DRG is linked to every inpatient stay and DRGs are designated using the principal procedure, principal diagnosis, age, discharge status and sex. Diagnoses and procedures assigned by using ICD-9-CM codes determine the DRG assignment. Thus, precise and complete ICD-9-CM coding by professionals is fundamental for adequate DRG naming and posterior reimbursement". "Before 1983, Medicare payments for hospital inpatient care were based on a retrospective reasonable cost system, which meant hospitals received 80 percent of reasonable charges. Since 1983, when the patient prospective payment system was implemented, Medicare has reimbursed hospitals for inpatient hospital services according to a predetermined rate for each discharge. Each discharge is categorized into a diagnosis-related group, which is based on the patient's principal and secondary diagnoses (comorbidities and complications) as well as principal and secondary procedures (if performed). The DRG determines how much payment the hospital receives and it is worth noting that ICD-9 codes directly affect DRG assignment and CPT codes play no role in DRG assignments. Diagnosis-related groups are organized into mutually exclusive categories called major diagnostic categories (MDCs), which are loosely based on body system (e.g., nervous system)" Green and Rowell (2007).

## **6.2.2 Current Procedural Terminology CPT**

"CPT codes are a coding system, defined in the publication Current Procedural Terminology, for medical procedures that allows for comparability in pricing, billing, and utilization review." Dictionary (2009) The American Medical Association (AMA) is maintaining the Current Procedural Terminology codes and holds also the registered trademarks rights of the CPT. Now a day it is the most common medical nomenclature to account medical services and treatments under private and public health insurance companies. American Medical Association (2010a)

"Although Medicare hospital inpatient payment rates are based on ICD-9 codes, Medicare's hospital outpatient payment system uses CPT codes to identify medical services. These outpatient services are grouped into ambulatory payment classifications, and CMS sets payment rates for each of these ambulatory patient classifications. The CPT codes also serve as the basis for other Medicare payment systems, including the Medicare physician fee schedule, the clinical laboratory fee schedule, and ambulatory surgical center payments. Payment rates are assigned to individual CPT codes

under the physician and clinical laboratory fee schedules.” Raab and Parr (2006a). Based on American Medical Association (2010d), the CPT code includes procedure set for:

- Physician services.
- Physical and occupational therapy services.
- Radiological procedures.
- Clinical laboratory tests.
- Other medical diagnostic procedures.
- Hearing and vision services.
- Transportation services including ambulance.

“The variety of medical treatments requires a very carefully handling of the codes and to keep attention of the details is a key to reduce confusion. Additional Information for the use of the code can be found in the headers or parenthetical statements” Nuwer (2009). Each CPT code has some associated dollar value. This value is differently calculated by different insurance companies based upon their plans under which the patients are insured. For physician’s office coding CPT codes decides the amount to be reimbursed to the physician based upon the physicians time, skill and risk involved with a particular procedure. Every physician bills his/her charges for services in the claim form. Different private insurance company reimburse different amount for the same procedure based upon their own fee reimbursement scheme and plans.

“Many new technologies do not raise coding issues. If a new technology is adequately identified by established codes, there is some probability that insurers have already made coverage and payment determinations that will apply to the new technology as well as the technologies that preceded it. In these situations, manufacturers know the reimbursement environment for the new technologies they develop. However, if a new technology, and the procedures associated with its use, represents an innovative approach not adequately captured by established codes, or if it confers additional benefits while costing more than the technology or procedures being replaced, new codes may be needed to distinguish it from previous technology, and the process of securing new codes can be both lengthy and complex” Raab and Parr (2006a). The Section 6.2.2 deals with the submission process for a new or changing an existing CPT code but before we can discuss this topic in detail, we have to talk about the different parties, which influence the application process. The Figure 6.3 on page 104 shows

the involved parties in the CPT code applying and changing process and the first two parties are described in a separate paragraph below.

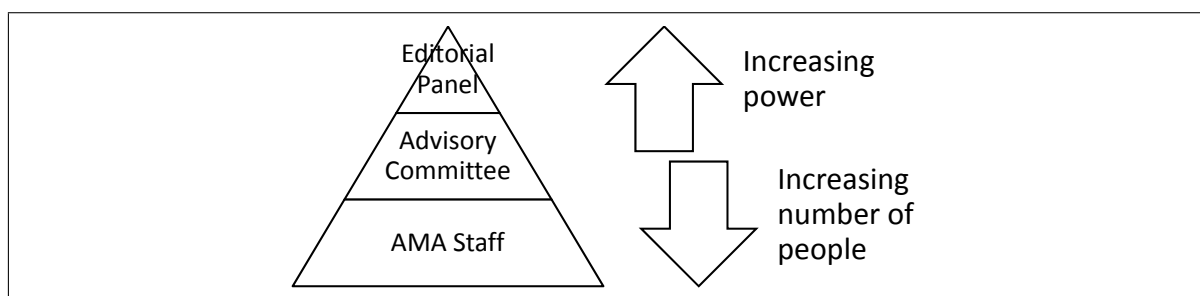


Figure 6.3: Involved parties in CPT changing process.

Afterwards, the content of the CPT Manual is explained and all three different categories of CPT codes are described in a separate paragraph. In end of this Section, we display the CPT code application process and also the relevant existing CPT code for SIGFRIED and EEG LI test.

**CPT Editorial Panel** The CPT Editorial Panel meets three times per year and deal with new technologies and upgrades of existing codes. “In total the Panel consists of 17 persons, 11 of these are physicians recommended by the Nation Medical Specialty Societies and accepted by the AMA Board of Trustees. The CPT Health Care Professionals Advisory Committee nominates two members the CPT Editorial Panel. Each of the following Association also designate one physician: the Blue Cross and Blue Shield Association, America’s Health Insurance Plans, the American Hospital Association, and the Centers for Medicare and Medicaid Services” cf.American Medical Association (2010d).

**The Advisory CPT Committee** The Advisory CPT Committee assists the CPT Editorial Panel during the Meetings and is preparing the details and special aspects of topics in forefront of the meetings. The Committee mainly consists of physicians selected by the various of specially national medical societies and at present the societies are restrict to members of AMA Health Care Professionals Advisory Committee (HC-PAC) and AMA House of Delegates. Also professionals with a performance measures background are supporting the CPT Editorial Panel, if it is necessary and requested. Based on American Medical Association (2010d), the next itemization lists the several objective, which are under the responsibility of the Advisory Committee.

- The most important task is to give advices on the nomenclature and procedure coding.

- The continuously documentation of the advices in particularly with regard to the adequacy use of the CPT code for the various of surgical and medical procedures.
- In an annually meeting the Committee discuss and review codes, which are getting a bit long in the tooth and need an update.
- The Advisory CPT Committee reviews the articles published by the AMA concerning the CPT code to provide information material particularly for new emerging technologies.

### **Current Procedural Terminology Manual**

Since 1966, the American Medical Association published a CPT Manual every year, which comprehend updates and changes of CPT codes as a result of significant improvement of medical practices and technology. The AMA released the CPT 2011 Professional Edition in October 2010 and the 760 pages dick spiralbound book costs about \$107.95. The book contains corresponding guidelines to the three different CPT categories and we explain every category in detail after a brief executive summary of them, based on OpenClinical (2010):

**Category I Codes** are designated for services (or procedures) common in contemporary medical practice and being performed by many physicians in clinical practice in multiple locations.

**Category II Codes** are used on performance measurement: Category II CPT codes are intended to facilitate data collection by coding certain services and/or test results that are agreed upon as contributing to positive health outcomes and quality patient care.

**Category III Codes** deal with emerging technology. The purpose of this category of codes is to facilitate data collection on and assessment of new services and procedures. These codes are intended to be used for data collection purposes to substantiate widespread usage or in the Food and Drug Administration (see Section 5.2) approval process.

**Category I CPT code** is used for well-established procedures and services. The category one codes are the bigger part of the CPT codes and people usually identify with this code when using the term CPT code. The code consist of five digits and starts with the number 00100 and ends with 99607. The Advisory CPT Committee the Category I codes ones a year and the codes are cut into six areas:

- 1 Evaluation and Management
- 2 Anesthesiology
- 3 Surgery
- 4 Radiology
- 5 Pathology and Laboratory
- 6 Medicine

As a condition, a procedure should be practiced by various doctors in several locations and up to date. The requirements for a CPT I codes are given by the Advisory Committees and the Editorial Panel and are listed below based on American Medical Association (2010d):

- that the service/procedure has received approval from the Food and Drug Administration for the specific use of devices or drugs
- that the suggested procedure/service is a distinct service performed by many physicians/practitioners across the United States
- that the clinical efficacy of the service/procedure is well established and documented in U.S. peer review literature
- that the suggested service/procedure is neither a fragmentation of an existing procedure/service nor currently reportable by one or more existing codes; and
- that the suggested service/procedure is not requested as a means to report extraordinary circumstances related to the performance of a procedure/service already having a specific CPT code.

**Category II CPT code** hold the codes concerning the evaluation for a physical process and the performance of services. A typical appropriation of a category II code is to account the assessment from clinical laboratory and radiology tests. Also the reimbursement for clinical or management services report the code and hence it should minimize the bureaucratic work for the medical staff. The code itself consists out of four digits followed by an F, but they are not designed for replacement of a regularly category I code. CPT Category II codes are arranged according to the following categories based on Merion Publications (2004):

- Composite Measures 0001F

- Patient Management 0500F-0503F
- Patient History 1000F-1002F
- Physical Examination 2000F
- Diagnostic/Screening Processes or Results 3000F
- Therapeutic, Preventive or Other Interventions 4000F-4011F
- Follow-up or Other Outcomes 5000F
- Patient Safety 6000F

**Category III CPT code** covers new rising technologies and comprises temporary codes for emerging procedures and services. The main idea behind the category III is to provide a billing basis for the face of data acquisition for the purpose of evaluation of a medical treatment. This evaluation can support the FDA certification process or show the clinic efficacy of the emerging technology. For this special purpose a few exceptions compare to the CPT code I requirements are done and listed below.

- The FDA approval must not be present
- Clinical efficacy has not to be proven
- A locally use of the treatment is accepted

As mentioned above, this conditions are especially helpful for an innovation hence this is the most likely category for our two diagnostic tests. Thus we will talk about this category more closer and in particular we precisely explain the Relative Value Unit (RVU) in a separate paragraph.

The American Medical Association provides the document “CPT Category III codes” on their Web site and this document gives a good overview about category III codes. The next paragraph highlights the most important parts of this document.

“CPT Category III codes are assigned an alphanumeric identifier with a letter in the last character (e.g., 1234T) and are located in a separate section of the CPT manual, following the Medicine section. It is worth noticing, that the inclusion of a service or procedure in a category III neither implies nor endorses clinical efficacy, safety, or the applicability to clinical practice, but the service/procedure must have relevance for research, either ongoing or planned. Because CPT Category III codes are intended to be used for data collection purposes to substantiate widespread usage or to provide documentation for the FDA approval process, they are not intended for services

or procedures that are not accepted by the CPT Editorial Panel due to an incomplete proposal, the need for more information, or a lack of CPT Advisory Committee support. The CPT Editorial Panel is in charge to set up a new CPT category III code and will publish them on a half-year basis on the official Web site. The releasing days are January 1st and July 1st. After the code is released the 6 month time period of implementation starts and so the code will be effective six month after published on the AMA Web site. This new codes will be print in the next CPT cycle edition. In Order to approve the new technology the CPT Editorial Panel needs information about the emerging technology and especially the CPT Advisory Committee plays a major role in the decision process. In the main after five years the codes are file away, unless it can show that it is still used in an appositely purpose” cf. American Medical Association (2009a).

**Appendix** After the category 3 codes, the CPT manual contains an appendix, that is numbered from A to M. The Appendix A consists of a list of 2 digit CPT codes called modifiers. Modifiers are appended to regular CPT codes in order to show the circumstances which cause deviation form the exact code description of a regular CPT code or to show some additional information to the insurance company so that correct dollar amount will be reimbursed according to the service rendered. The Appendix B consists of a summary of additions, deletions and revisions in the CPT manual of the current edition over that of CPT manual of the last year. The Appendix C consists of a list of clinical examples to ensure the understanding of certain CPT codes and Appendix D contains a summary of add-on codes.

**Add-on codes** Codes with a + symbol in the category I CPT codes are all add-on codes. Certain listed procedures of CPT are commonly carried out in addition to the primary procedures performed. These additional or supplemental procedures are designated as add-on codes. For Example the CPT code 19000 is for Puncture aspiration of cyst of breast. If more than one cyst us aspirated then add-on code + 19001 is used to report aspiration of each additional cyst as many cyst aspirated. Here the primary code is 19000 and its add-on code is 19001. Add-on codes are never reported as stand-alone or primary code, because they always have to used with their designated primary codes together.

### **Applying for a CPT code**

In the last section we talked about the CPT Manual and we explained the Manual’s content. Generally, it is not expected to find an existing CPT code that matches for

a new technology. Therefore a development result normally needs a new or modified CPT code to be entered into the payment billing system. Thus this subsection deals with the application process for a new or to modify an existing CPT code and we stress on the category I and III codes, because they are relevant for our two development results. This subsection is split up into two main parts: who decides the request and which factors count for the decision. Second, we talk about the Coding Change Application Form and about additional information which should be submitted with this form. During the Editorial Panel meeting, the CPT application are discussed by the panel and also they come to a decision, whether a new CPT code application is approved or declined. The Editorial Panel gets support for the CPT/HCPAC Advisors, who review the code change requests. Also relevant clinical literature is considered in the final decision. The whole meeting is organized and managed by the CPT staff and also the necessary information for a request of CPT codes change must be submitted to the CPT staff 30 days in advanced of the Meeting.

In the most cases it is very useful to submit the application for a code change in corporation with the relevant medical societies, because the societies support the code change request in terms of consistency and coherency. In addition, the societies make sure that the requested code is not contradictory to existing codes and we discuss the role of the American Academy of Neurology in a separate paragraph below. It is important to mention, that the American Medical Association also formulated a clear statement that the supporting role of the medical societies and especially of their advisors has nothing to do with lobbying. But they explicit forbid any kind of unsolicited communication both with the CPT/HCPAC Advisors and members of the Editorial Panel. Because of these, every information should be submitted the CPT staff and not directly to the CPT/HCPAC Advisors or members of the Editorial Panel. Only during the open meeting a comment in front of the full Editorial Panel or a directly request of a Panel member is permitted.

**The Role of the American Academy of Neurology (AAN)** The support of the corresponding society is essential for the success of a changing or new code request and for both SIGFRIED and EEG LI test, the American Academy of Neurology is the expedient society. An early cooperation with the society can be beneficial and the next citation expresses, how the AAN participates in the application process. “The American Academy of Neurology will send one or two so called CPT Advisors to the CPT Editorial Panel, when a new relevant code application is deposited. The CPT Advisors are members of the Academy’s Coding Subcommittee of the Medical Economics and Management Committee, which oversees reimbursement, billing, and coding pro-



cesses. These advisors will act as topic experts in particular during the oral discussion when the code request is debated” Nuwer (2009).

**Coding Change Application Form** The AMA provides a form to submit an application for a new code or either a change of an existing code. The form is available at the AMA Web site (<http://www.ama-assn.org/>). The AMA suggests to make yourself first familiar with the Fourth Edition of the Current Procedural Terminology before filling out the application form. There are also several guidelines developed by the AMA which should simplify the requesting process. The article “*Applying for CPT Codes*” formulates the criteria for development and evaluation of CPT Category I and Category III codes and is cited below.

In developing new and revised Category I codes the CPT Advisory Committee and the CPT Editorial Panel require the following conditions based on American Medical Association (2010b):

- that the service/procedure has received approval from the Food and Drug Administration (FDA) for the specific use of devices or drugs;
- that the suggested procedure/service is a distinct service performed by many physicians/practitioners across the United States;
- that the clinical efficacy of the service/procedure is well established and documented in U.S. peer review literature;
- that the suggested service/procedure is neither a fragmentation of an existing procedure/service nor currently reportable by one or more existing codes; and
- that the suggested service/procedure is not requested as a means to report extraordinary circumstances related to the performance of a procedure/service already having a specific CPT code.

The following is used as formalized criteria by the CPT Advisory Committee and the CPT Editorial Panel for evaluating Category III code requests and includes identification of the following elements as guidelines for establishment of a Category III code based on American Medical Association (2010b):

- A protocol of the study or procedures being performed;
- Support from the specialties who would use this procedure;
- Availability of United States peer-reviewed literature for examination by the Editorial Panel;

- Descriptions of current United States trials outlining the efficacy of the procedure.

The submitter of an application should contemplate the following aspects. First, the candidate should make clear if there is any currently existing code, where the new procedure or service could be included without significantly changes to the extent of the code. Second, the submitter should define whether it is a variation or fragmentation of an existing code or either a complete new code. In this context it is very important to document why an existing code is not adequate for the service or procedure and also keep in mind the opportunity to use several existing codes to bill the new technology. Hence, this should include a statement which verify that new technology is a distinct service. In this regard an estimation of how many physician might use this procedure or service and where it is performed can back up the argumentation. The following list contains all necessary information, which should be submitted to the CPT staff in addition to the coding change application form and the itemization is based on American Medical Association (2010c):

- a complete description of the procedure/service (eg, describe in detail the skill and time involved. If this is a surgical procedure, include an operative report that describes the procedure in detail);
- a clinical vignette which describes the typical patient and work provided by the physician/practitioner; the diagnosis of patients for whom this procedure/service would be performed;.
- a copy of the diagnosis from potential patients for the new procedure or service
- a copy(s) of peer reviewed articles published in US journals indicating the safety and effectiveness of the procedure, as well as the frequency with which the procedure is performed and/or estimation of its projected performance; and
- additional literature, which support the request relating to policy statements and guidelines.
- evidence of FDA approval of the drug or device used in the procedure/service if required.
- national statistical data about the procedure or service

**Clinical Vignette** For every code change request a clinical vignette must be submitted with the application. The clinical vignette should show which persons typically will receive the new treatment. The guideline *“Sample Format for Required CPT Clinical Vignettes”*, which is available on the AMA Web site, contain the following example.

“Current Procedural Terminology code ➔ 61863: Twist drill, burr hole, craniotomy, or craniectomy with stereotactic implantation of neurostimulator electrode array in subcortical site (eg, thalamus, globus pallidus, subthalamic nucleus, periventricular, periaqueductal gray), without use of intraoperative microelectrode recording; first array.

**Typical patient:** A 66-year-old woman presents with a ten-year history of idiopathic Parkinson’s disease that has caused progressive disability. She continues to respond to antiparkinson medications, however; her symptoms are no longer adequately controlled with medications and she is experiencing disability for many activities of daily living. Medication adjustments and different medication regimens have failed to improve her level of disability.

**Description of procedure(s)/service(s):** She undergoes implantation of a stereotactically-guided deep brain stimulator electrode array in the subthalamic nucleus using macro stimulation for targeting and confirmation of electrode placement” American Medical Association (2010e).

### 6.2.3 Relative value unit

“CPT Category III codes are not referred to the AMA-Specialty RVS Update Committee (RUC) for valuation because no relative value units (RVUs) are assigned to these codes. Payment for these services or procedures is based on the policies of payers and not on a yearly fee schedule” American Medical Association (2009a). “Fortunately, the CMS is mandated to publicly announce, through the Federal Register, the anticipated fee schedule for the following year. This is done first in a “proposed rule,” usually distributed during the summer (June or July). A comment period follows, allowing specialty societies, individual physicians, and others to review any proposed changes in the fee schedule and the rationale behind those changes. The CMS staff must then consider these comments and construct a “final rule” that is published in November or December, which establishes the actual fee schedule for the following year. Using the RVU values in that schedule, each of the Medicare carriers and private payers can construct an actual payment schedule for the coming year” Thorwarth (2004).

In to the “Federal Register / Vol. 66, No. 212 / Final rule with comment period”, the CMS states their position regarding to the reimbursement policies of payers. “Commenters expressed appreciation for our recognition of these new categories of CPT codes. However, one commenter believed that we should refrain from categorically denying payment for category III (emerging technology) CPT codes, because these CPT codes may sometimes warrant payment. Another commenter believed that we were proposing not to pay for these codes at all. The commenter recommended that we clarify in the final rule that carriers may determine if payment should be made for

a particular emerging technology code. Response: We believe that these codes will serve an useful purpose. We regret that some commenters believed that the discussion in the proposed rule implied that these services should not be covered. We only intended to indicate that by publishing these codes we are not indicating that we would pay for these services in all instances. As the commenter indicates, coverage of emerging technologies and payment for these services is at the discretion of the carriers. We also want to clarify that our carriers will be able to incorporate these codes only after they are entered into our system during our regularly scheduled updates and not as soon as the AMA posts them on the CPT web site” Centers for Medicare & Medicaid Services (2001).

**Time line and cost estimation** The goal for an innovation is to be assigned with a reimbursement code that guaranties adequate amount that can be reimbursed. The ICD-9 codes are used to reimburse hospital utilization for inpatient diagnoses and procedures. The CPT code is used for both hospital utilization for outpatient diagnoses and procedures, and for physicians fees. The flowchart diagram (Figure 6.4) summarizes and displays the CPT codes applying process.

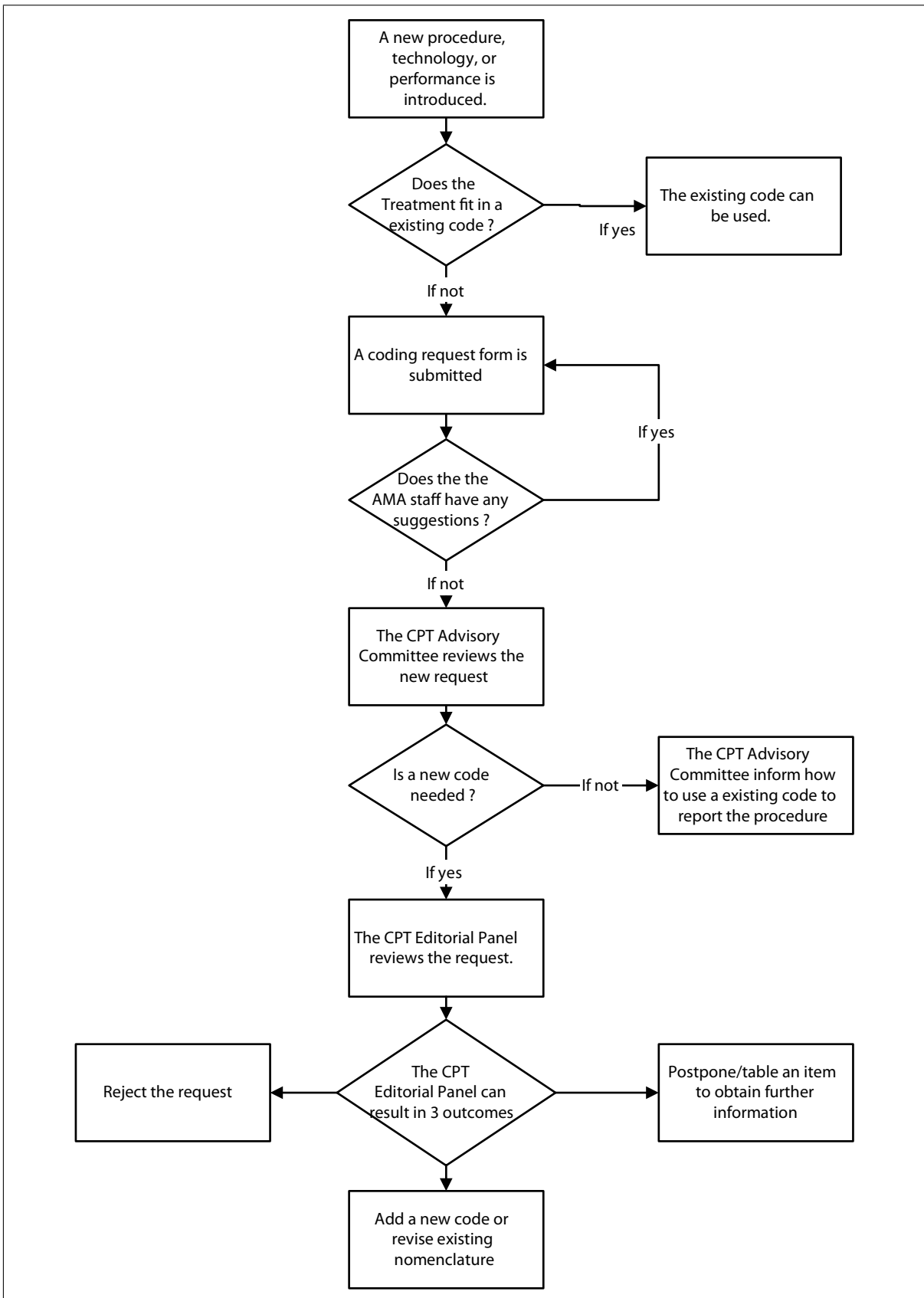


Figure 6.4: Flowchart diagram of CPT code application process.

According to Table 6.1 on page 115, an expansion of existing technology needs one

to two years post-FDA approval.

	Similar to another product	Expansion of existing technology	Truly new and innovative
Reimbursement components that must be developed	Confirm existing code and inclusion for coverage of this product	Alter coverage, coding, and payment to include this product	Create new coverage, coding, and payment for this product
Science required	Usually FDA approval for same indications suffice for inclusion in existing coverage	Publication of controlled studies (usually 1-2)	Publication of controlled studies (usually 2-4) and cost-effectiveness data (publication and/or registry data)
Typical time line for these components post-FDA approval	6 months to 1 year	1 to 2 years	2 to 5 years

Table 6.1: Overview of reimbursement’s time line for development results. “The last row estimates the time line for obtaining both coverage determination and reimbursement code, after the product is approved by the Food and Drug Administration (FDA)” Becker and Whyte (2006).

“Indication expansion of an existing technology often requires altering coverage, coding, and payment to address the new indication. Published studies supporting the proposed additional indication and revisions of established medical policy will be necessary to create coverage. Codes may need to be revised, including new code descriptions, which can trigger different payments rates” Becker and Whyte (2006).

Both development results match this description, and hence both are in a range between one and two years, but there are minor differences in the argumentation of the terms reasonable and necessary. These terms are the major criteria for the local coverage determination, and papers that support the argumentation for these criteria are helpful in this regard. For the EEG LI test, several papers call the current gold standard, Wada-test into question. For examples, in 2002, the journal NEUROLOGY published the article *“Is it time to replace the Wada test?”* by Abou-Khalil and Schlaggar (2002). In 2003, an article with same title was published in the same Journal, but with different authors Baxendale et al. (2003). We assume that the EEG LI test will need 1.25 years to pass the reimbursement process.

Currently, SIGFRIED improves the electrocortical stimulation procedure, and the value of the improvement is not as widely accepted as for EEG LI test. Thus, more detailed documentation of the improvements is required, and we assume that the reimbursement process will need 2 years for SIGFRIED.

For accomplish reimbursement coverage, the ideal qualification of the responsible person is a master in software engineering and the Table 5.2 on page 87 provide the expenses to employ a software engineer. For EEG LI test, the product of the software engineer personal cost multiplied by the necessary time results in \$262,469 and for SIGFRIED, the reimbursement process cost is \$419,950.

## 6.2.4 Summary of reimbursement code

The next two paragraphs summarizes the relevant reimbursement code issues for the two clinical diagnostic tests.

**SIGFRIED** is performed in an inpatient setting and it takes place in a hospital such as a Fourth–Level Epilepsy Center. For inpatient care, the Medicare companies do not pay for every device separately, instead the hospital receives a bundled payment amount based on the diagnosis related group (DRG). DRG payment are linked to ICD-9 codes, which identify surgical procedures. If a ICD-9 code that describes electrocortical stimulation is sufficient to include SIGFRIED into the procedure than the hospital can obtain reimbursement for SIGFRIED. In this case, SIGFRIED does not need a separate code to be identified. If not sufficient ICD-9 codes exists, the manufacturer needs to seek a new ICD-9 code, which includes appropriate DRG assignments for the new ICD-9 code.

**EEG LI test** is executed in the hospital outpatient setting, which requires to use CPT codes to identify the procedure. The Medicare companies also combined the CPT codes into payment bundles, which are called ambulatory payment classification. This classification pays the hospital a presumably amount for the facilities costs, which equals the procedure's technical item fees for the performed procedure.

The physicians, who execute the procedure, also need to use the CPT code to identify the performed procedure because their fee is also based on the CPT code. It is worth noticing that hospitals are paid separately from physicians.

## 7 Competitive advantage

At this stage, our development results already went through the FDA approval, Medicare coverage decision and applying for a reimbursement code procedure. In other words, the manufacturer owns a product that can be sold to a hospital and private physician and these health care practitioners would be reimbursed by Medicare companies for their treatments. Thus, the last missing step is the actual purchasing-decision process between the hospital or private physician and the manufacturer. Economically, the success of a development result is measured in profit and the revenue has a linear impact on the profit. The number of sales are affected by the outcome of purchasing-decision process and the purchasing process can be complex and time consuming because several parties are involved in the purchasing decision. Especially in large organizations such as a hospital, it is difficult to determine every influencing party and factor of the purchasing-decision process. This chapter deals with the decision-making units and impact factors of the medical device purchasing process.

**Aspects of hospital purchasing-decision** The paper focuses on the cognitive and organizational factors and The article *“Institutional decision-making to select patient care devices: identifying venues to promote patient safety”* by Keselman reports the purchasing-decision process in a large urban hospital for the item infusion pump and we reference to this article through the whole section. In the paper’s introduction, the author gives an overview of the relevant influence factors and their connections. The Figure 7.1 on page 118 outlines potential (hypothesized) relationships among various factors that may affect the process of institutional medical device selection and the purchasers perception of the process.



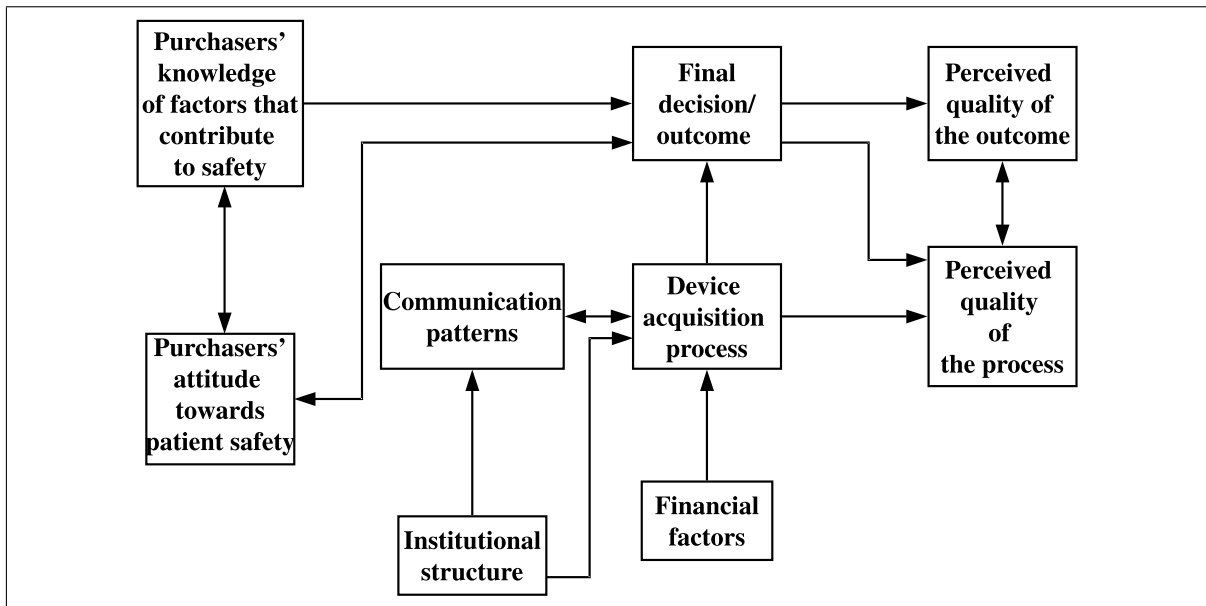


Figure 7.1: Aspects of hospital purchasing-decision. “The boxes represent aspects of the decision-making process and factors that influenced these. The arrows show the directionality of causal relationships among the different factors” Keselman et al. (2003).

“The design of the framework involved both theoretical and empirical processes. Following a systems approach to medical errors, we chose to focus on the institutional structure, communication patterns, and financial factors as contributors to the process. The study’s focus on patient safety and research on medical decision-making lead us to include purchasers’ knowledge and attitudes towards patient safety, as well as their perception of the process and the outcome” Keselman et al. (2003).

**Decision-making unit** Every decision to purchase a product or service is influenced by one or more members of the so-called decision-making unit (DMU). Based on Morse (1998), this comprises:

**User:** the person who will use the product or service

**Influencer:** usually someone whose advice is requested or offered which as a result can influence the brand, the manufacturer, price, timing, etc, of the purchase.

**Decision maker:** the ultimate maker of the decision to purchase the service or product (remember that it can be a committee).

**Buyer:** the purchasing officer who has responsibility for the purchasing budget and therefore of getting the best value for money.

**Gatekeeper:** literally he or she who controls access to the rest of the decision-making unit: perhaps an information provider, a secretary or a security manager.

Keselman reported in his article the following DMUs: “Professionals with three types of expertise-administrative, engineering, and clinical-were involved in the selection pro-

cess. Three administrative/technical departments played a major role in device selection: Purchasing, Support Services, and Engineering and they are displayed in Figure 7.2

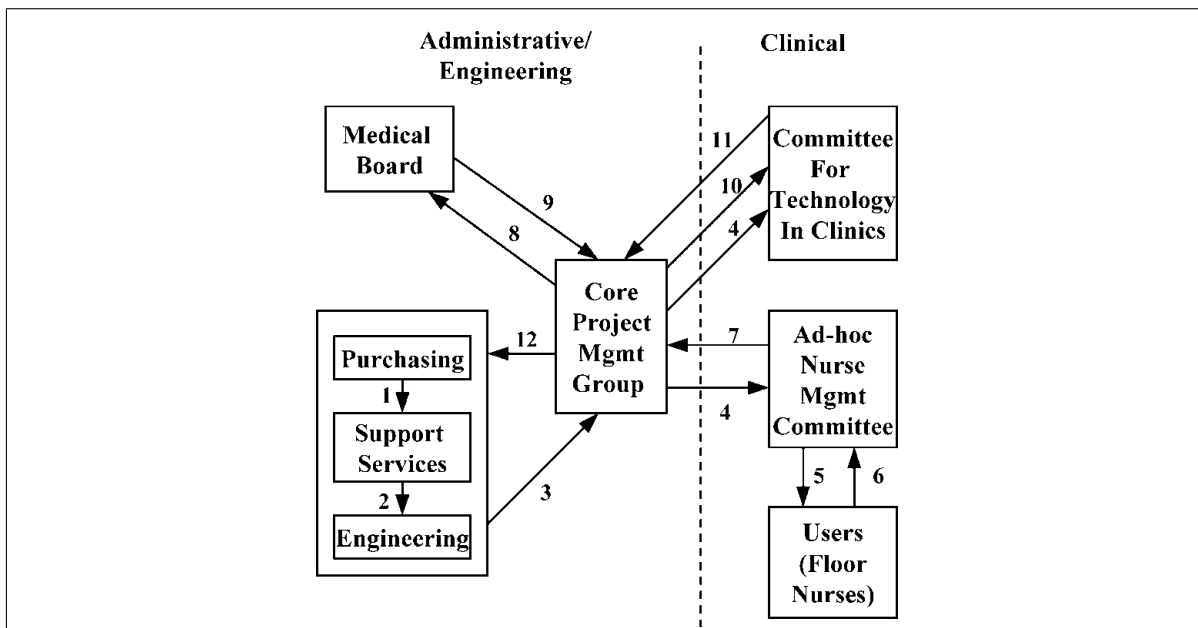


Figure 7.2: Decision-making flowchart. “The blocks in the figure represent different groups and committees that participated in the process. The numbered arrows represent the direction of information flow (from the transmitter to the receiver of the primary information). The dashed line separates participating groups with administrative and engineering expertise from participating groups with clinical expertise” Keselman et al. (2003).

The function of the Purchasing is to supervise and negotiate financial agreements. Support Services deals with the distribution of supplies and devices within the hospital and provides liaison between top-level administrators and clinical personnel. Engineering is responsible for technical maintenance of equipment. Individuals from these departments formed the Core Project Management Group that led the selection process.

Two clinical groups participated in the selection process. The Committee for Technology in Clinics is a standing committee that includes high-ranking physicians, engineers, and administrators. The committee reviews and formally approves all technology acquisitions in the hospital. The second clinical group was an ad-hoc committee that included nurse managers from major hospital units that used infusion devices. The infusion pump is a device that is primarily used by floor nurses. Since core project managers did not directly interact with floor nurses, they relied on Nurse Managers’ Committee to provide the liaison with the users” Keselman et al. (2003).

## 7.1 Time line and cost estimation

The last two sections reviewed the numerous factors and parties involved in the decision process. Figures 7.1 and 7.2 in particular highlight the complexity of the process, and hospitals had to yet developed a standardized purchasing process. Hence, every hospital has its own purchasing procedure, which is not transparent to the public and entails unpredictable delays. As a Reference, we use the case study published by Keselman et al., and the Table 7.1 on page 120 is cited from this study.

Event	Date
Announcement of Vendor B s new model release	11/18/96
Price estimate negotiated with Vendor B; clinical trials planned at campus 1	1/13/97
Pump B evaluation completed at campus 1	11/24/98
First mention of Vendor A; plans to trial both pumps at both sites	1/12/98
Both vendors present financial proposals	4/27/98
Trials completed on both campuses	10/19/98
Purchasing administration meets with the leadership on both campuses	3/22/99
Pump B chosen by administration; committee endorses decision	5/17/99
The total duration of the purchasing-decision process was approximately	<b>2.5 years</b>

Table 7.1: “Time of purchasing-decision process” Keselman et al. (2003).

“Figure 7.1 presents major selection process events and the process starts with consideration of one option, Vendor B’s new model. The model is chosen from a familiar vendor, and the purchasers quickly proceed to financial negotiations, and then clinical evaluations. It is only after significant shortcomings are found in Pump B the second candidate comes under consideration. Next, preliminary negotiations with both vendors establish that the new candidate costs 8% more than Pump B. Both pumps are clinically evaluated on both campuses and the Core group administrators selected the less expensive model” Keselman et al. (2003).

In this study, the decision-making process needed approximately 30 months and both products were almost similar. In the end, it came down to a financial decision. We assume that the purchasing-making decision time for products, that have a clear advantage compared to the concurrent, is shorter and less complex. As a rough estimation we assume that:

Development result	Purchasing-decision time [years]
EEG LI test	1.2 years
SIGFRIED	1.8 years

Table 7.2: Estimated purchasing-decision process's time of the two diagnostic tests. Both numbers are rough estimations, because a details evaluation of these numbers is not possible at this early stage of the innovation process. But, it is important to include purchasing-decision time into the overall picture of the innovation process to have a complete picture.

EEG LI test is an independent device, and it is based on a well established, non-invasive, and safe technology (EEG recording). Furthermore the EEG LI test's attributes compared to the current gold standard, the Wada test, are significantly better (see Table 3.9 on page 39). Hence, we assume for EEG LI test a short purchasing-decision time of 1.2 years.

The invasive method SIGFRIED is more complex than the EEG LI test, so the purchasing-decision process involves more parties. Thus, we estimate for SIGFRIED a purchasing-decision time of 1.8 years.

**cost** A marketing manager is the right person to supervise the purchasing process, and Table 7.3 presents the annual costs for a marketing manager at the Wadsworth Center.

Marketing manager				
Base Salary	Fringe rate	Fringe cost	Indirect cost	Total
89,000	37.50%	33,375	85,064	207,439

Table 7.3: Marketing Manager salary. This table shows the total costs incurred by the Wadsworth Center to employ a marketing manager with several years of experience. All numbers are in USD per year.

The product of the total personal cost per year times the required years equals the total expenses of the hospital purchasing decision. Hence, the Wadsworth Center has to spend for SIGFRIED \$373,388 and for EEG LI test \$248,927 to sell the diagnostic tests to a hospital.

## 7.2 Benefits of development results

A development result should address the customer's needs better than the existing competitors on the market, and the customers for both development results are hospi-

tals and private physicians. At the current stage, a detailed evaluation of the purchasing-decision process is not possible, because every hospital has a different process, and the first target customers have not yet been identified. In general, the hospitals base their purchasing decisions on the same factors and this section ranks factors that influence the hospital's purchasing decision. Afterwards this section shows that the two clinical diagnostic tests address the influence factors of hospital purchasing decision better than the established methods.

The article "*The Role of Patient Safety in the Device Purchasing Process*" by Johnson et al. (2005) concludes that *patient and user safety* is the major impact factor followed by *clinical reasonable*. Furthermore *cost-effectiveness* is more important than *easy of operation*. Note that ease of operation should not influence the correct handling of the device. Especially for software, tools that are not easy to operate can lead to safety concerns. For example, if the graphical user interface is not arranged clearly, then users may apply incorrect settings that lead to erroneous outputs. In our ranking, ease of operation did not interact with safety concern and is arranged behind *being a technological leader*. "Because being a *technological leader* is graded as a strong factor in the purchasing-decision process" cf. Teplensky et al. (1995).

1. Safety
2. Clinical reasonable
3. Cost-effectiveness
4. Being a technological leader
5. Easy of operation

**Safety** Because EEG LI test is a completely non invasive procedure, it raises no safety concerns. "The established method, the Wada test had a 0.7% risk of carotid artery dissection" cf. Loddenkemper, Morris and Perl (2002).

Compared to the electrocortical stimulation, SIGFRIED does not actively stimulate the cortex, and hence SIGFRIED does not raise any risk of seizure induction.

**Clinical reasonable** For both diagnostic tests, the conducted studies demonstrated that the tests results are in consensus with the established methods. Thus they are as reasonable as the current gold standard.

**Cost-effectiveness** The Table 3.10 on page 43 points out that the costs, which occur that the hospital's costs are 23 times lower for an EEG LI test than for fMRI, and the

Wada test costs about 3.8 times more than fMRI. Thus, the EEG LI test has significant cost advantages against both the established method (the Wada test) and the dominant emerging technology, fMRI.

**Being a technology leader** Both development results are based on the novel technique Brain Computer Interface and especially SIGFRIED already gained attention of different journals and museums. For example, the American Museum of Natural History shows SIGFRIED in a special brain exhibition and published an article about SIGFRIED in the Fall 2010 edition of the museum's journal Rotunda.

**Easy of operation** Because the final graphical user interface is in the development phase, it is not possible to compare them yet. But the responsible software engineers are aware of this point and they will stress on the easy to operation factor in further improvements.

### **7.3 Summary of competitive advantage**

This chapter demonstrated that the purchasing decision-making process is time consuming, because hospitals are complex organizations and several different parties are involved in the purchasing decision. The personnel cost estimations conclude for SIGFRIED \$373,388 and for EEG LI test \$248,927 to accomplish the purchasing decision between the manufacturer and the hospital. Furthermore, this chapter highlighted that these novel clinical diagnostic tests address all hospital purchasing decision factors significantly better than competing technologies. Hence, hospitals are likely to purchase these new clinical diagnostic tests.

## 8 Conclusion

Two common medical procedures - language lateralization and functional brain mapping - currently require procedures that are invasive, time consuming, expensive, and rely extensively on medical experts. By capitalizing on rapid progress in BCI systems and other related technologies, as well as the extensive experience developing BCIs for patients, the BCI2000 group at Wadsworth center has developed new BCI technologies that can perform these two procedures. The new technologies are noninvasive, faster, cheaper, and much easier to use even for staff without medical training. We developed a plan to exploit the two recently developed clinical diagnostic tests, which we summarize in the following time line.

**Time line** Four of the chapters address four topics: results at the Wadsworth Center; regulatory environment; reimbursement policies; and the hospital purchasing decision process. These four topics correspond to four phases in the pre-commercial development process for the two novel diagnostic tests.

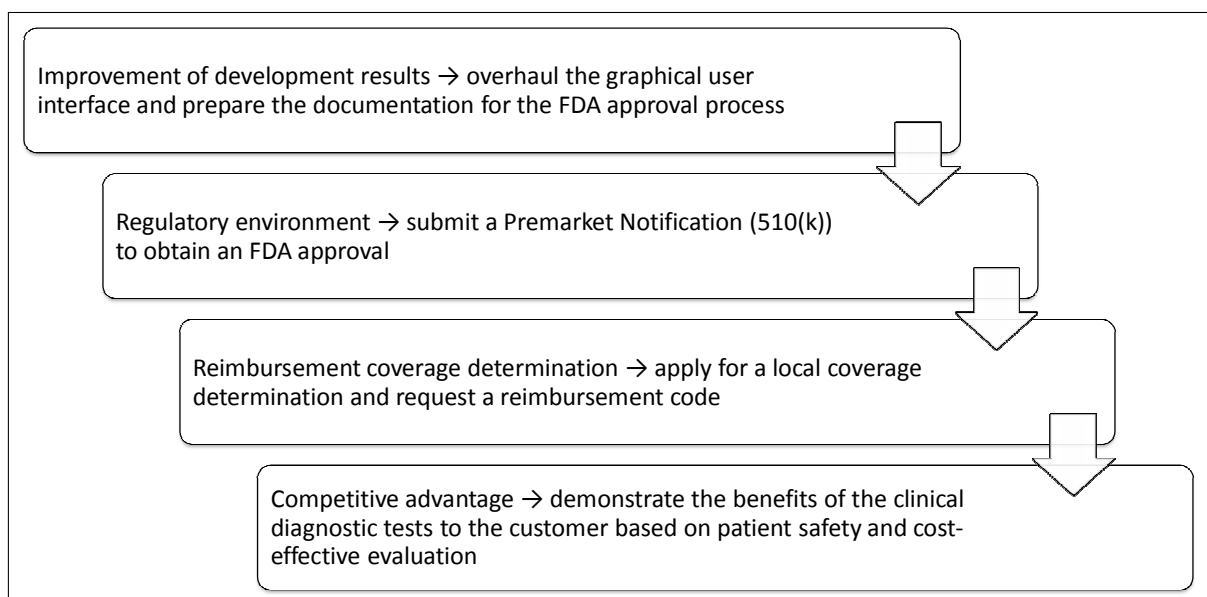


Figure 8.1: Outline of the pre-commercial development. The work's structure is in accordance with this figure.

Figure 8.1 summarizes these four phases and the Table 8.1 shows the total time effort that is necessary to accomplish the four milestones in terms of person years.

Task	EEG LI test	SIGFRIED
Improvement of development result	1.65 years	1.65 years
Regulatory environment	0.25 years	0.25 years
Reimbursement	1.25 years	2.00 years
Hospital purchasing decision	1.00 years	1.50 years
<b>Total</b>	<b>4.15 years</b>	<b>5.40 years</b>

Table 8.1: Total time effort. Estimated time line for SIGFRIED and EEG LI tests. Note that some rows reflect variable time costs. For example, the top row reflects that 1.65 years are necessary, but hiring additional staff could reduce this time considerably. Furthermore, some stages can overlap each other, which is called “simultaneous engineering” and is common in such projects. Hence, these estimates are quite conservative and reflect more the total effort required more than the minimum duration of the innovation process.

The Figure 8.3 illustrates the time line for SIGFRIED and Figure 8.3 displays the time line for EEG LI test to reach the market. These Figures are based on the assumption that two software engineers are working at the same time to improve the development result and only one person works on reimbursement and hospital purchasing decision at the same time. The waiting time depict the time which is necessary to finish the preconditions for the specific task. After the improvement of the development result is finished it is possible to start with the FDA application and reimbursement coverage determination at the same time. For both inventions, it is reasonable to start with the hospital purchasing decision after a positive coverage determination is predictable and we assume 1.5 years. Simultaneous engineering saves time but on the other hand it requires additional workforce. The pre-commercial development time line of SIGFRIED and EEG LI test uses simultaneous engineering, because of the short lifetime cycle of software it is reasonable to cut off the pre-commercial development time.



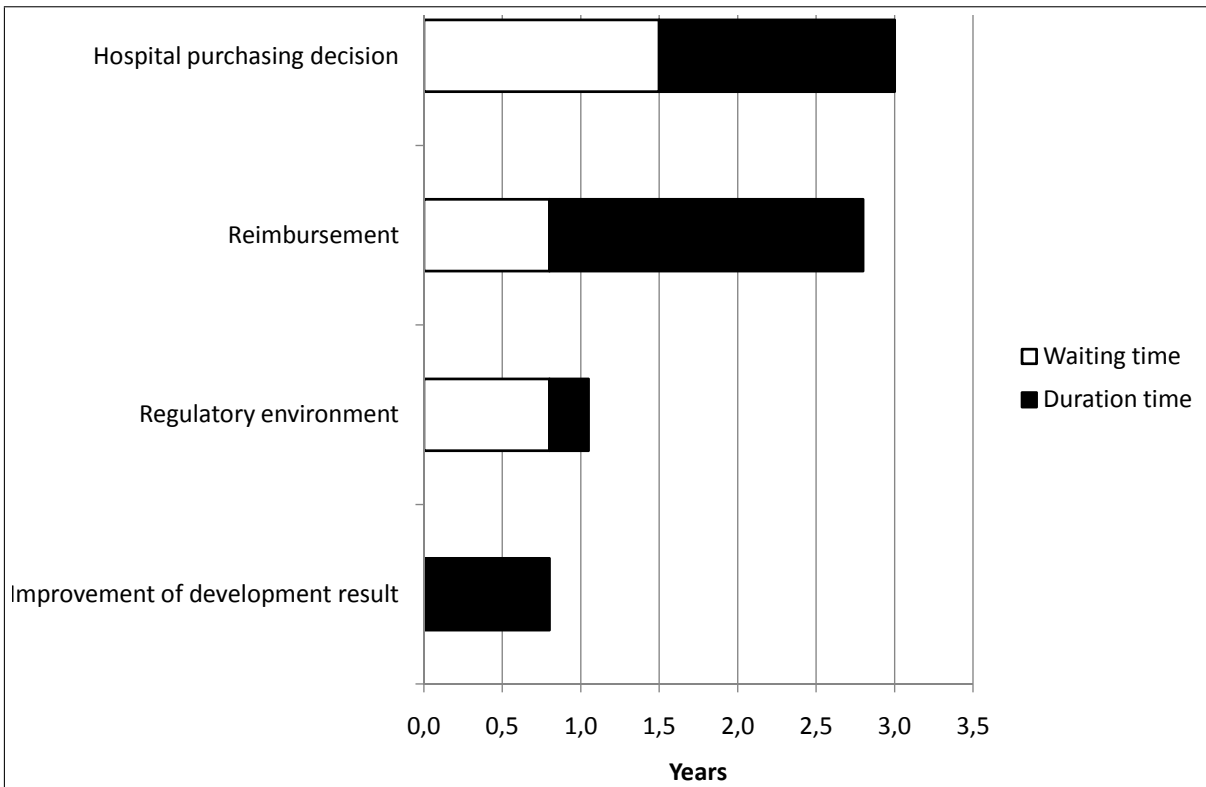


Figure 8.2: Pre-commercial development time line of SIGFRIED.

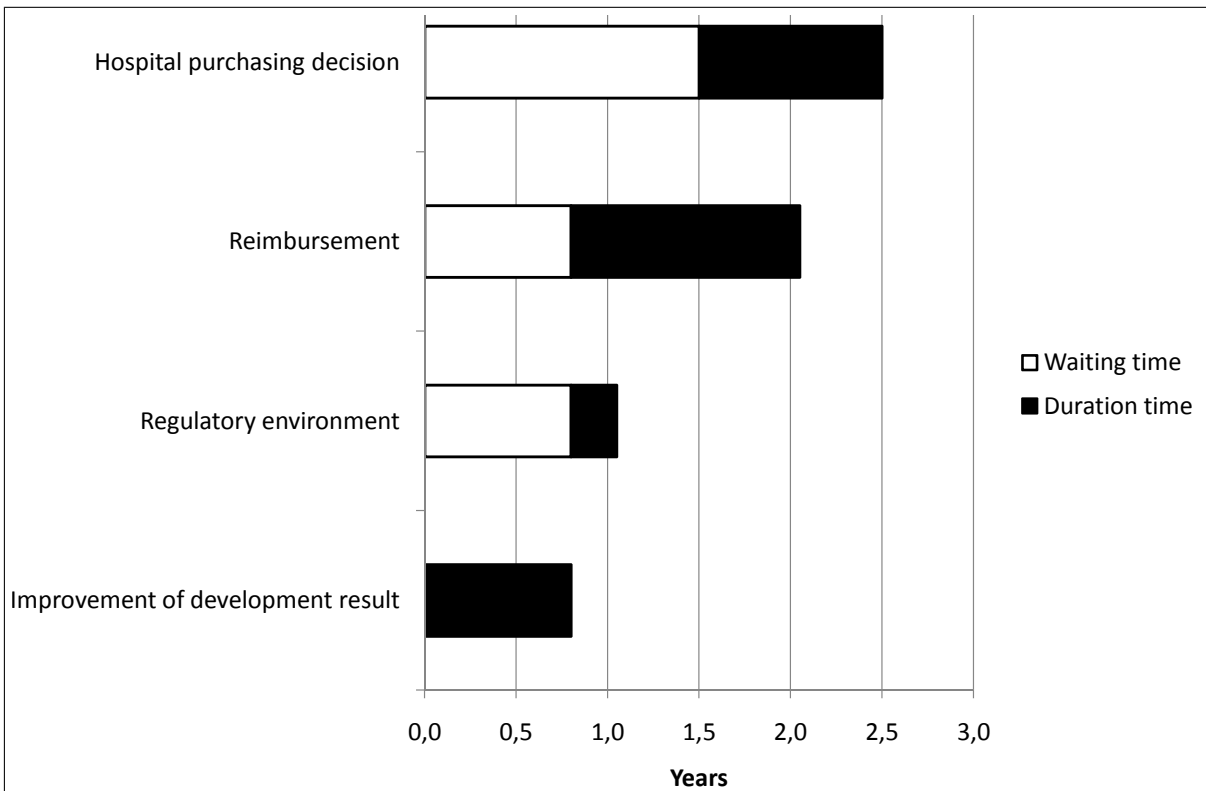


Figure 8.3: Pre-commercial development time line of EEG LI test.

**Pre-commercial development cost** Based on the time lines, the Table 8.2 estimates the pre-commercial development cost for SIGFRIED and EEG LI test.

Task	EEG LI test	SIGFRIED
Improvement of development result & regulatory environment	\$402,646	\$402,646
Reimbursement	\$262,469	\$419,950
Hospital purchasing decision	\$248,927	\$373,388
<b>Total</b>	<b>\$914,042</b>	<b>\$1,195,984</b>

Table 8.2: Total pre-commercial development cost. This Table estimates the pre-commercial cost time for SIGFRIED and EEG LI tests to sell the clinical diagnostic test to hospitals.

In order to calculate the total pre-commercial development cost per unit, it is necessary to estimate the total number of products that will be sold. In chapter 4, the available market is estimated for both inventions and the following assumption is made: The penetrated market, which is the set of consumers who are buying the company's product, is a half of the available market. In other words, 50% of the available market customers actually purchase the medical device. The Table 8.3 contains the pre-commercial development cost per unit based on the assumed penetrated market.

Clinical diagnostic test	Development cost per product
SIGFRIED	\$11,446
EEG LI test as pre-surgical procedure for brain surgery	\$6,554
EEG LI test as neurological assessment battery	\$182

Table 8.3: Pre-commercial development cost per unit based on estimated penetrated market.

For SIGFRIED and EEG LI test, the Table 8.4 forecasts the product cost that contains pre-commercial development cost, software cost and hardware cost.

	SIGFRIED	EEG LI test as pre-surgical procedure for brain surgery	EEG LI test as neurological assessment battery
Pre-commercial development cost	\$11,446	\$6,554	\$182
Software cost	\$1,200	\$1,200	\$1,200
Hardware cost	\$22,138	\$21,338	\$21,338
<b>Total cost</b>	<b>\$34,784</b>	<b>\$28,881</b>	<b>\$22,720</b>

Table 8.4: Estimated product cost.

The numbers in Table 8.4 does not include all arising expenses for example overhead, marketing, assembly or installation cost are missing. But, the numbers provide a first indication of the direct related product cost.

**Summary of technology exploitation** This thesis discusses the economical aspects of the inventions EEG LI test and SIGFRIED, which have been developed by the Wadsworth Center. EEG LI test provides benefits as neurological test battery and as a presurgical procedure examination for resective brain surgery. On the hand, SIGFRIED can only be sold as a presurgical procedure test for resective brain surgery. The two clinical diagnostic tests are ready for further development and technology exploitation. The development results have been tested in both laboratory and field environments, by practicing research scientists and medical experts, and upgraded accordingly. The conducted studies proved that both clinical diagnostic tests are safer and less time consuming than the current established methods. Both tests provide large cost-reducing potential compared to the gold standards, because fewer medical personal are needed to perform them.

The next steps involve appropriate certification, reimbursement coverage determination and final purchasing decisions of hospitals and private physicians. For EEG LI test, this work estimates that it takes  $2\frac{1}{2}$  years to accomplish the mentioned steps and these steps cost \$914,042, which include personnel expenditures and application fees. The available market as neurological test battery contains 9668 private physicians and 279 hospitals. Assuming that 50% of the available market customers purchase the development result EEG LI test, pre-commercial development cost per unit is \$182 as neurological test battery and \$6,554 as pre-surgical procedure for brain surgery. For SIGFRIED, this thesis assumes that it takes 3 years to finish pre-commercial development and to launch the invention at the market. The expenses for that are estimated at \$1,195,984, includes personnel expenditures and application fees. If 50% of the 209 hospitals that are forecasted as available market buy the clinical diagnostic test SIGFRIED then the pre-commercial development cost amounts \$11,446 per unit. Both EEG LI test and SIGFRIED can fetch a retail price of \$40,000–\$50,000 per software package, excluding the hardware, hence the margin of profit is adequate to serve all stakeholders like inventor, manufacturer, Medicare company and hospital.

This work proved that both inventions are economically feasible and that they have what it takes to become accepted as innovations. The ongoing efforts will continue to show that the development results are superior to the current gold standard technologies in various ways, and hence - with an appropriate exploitation plan - could become the new de facto standard for critical aspects of common neurosurgical procedures. As an FDA approved and qualified for reimbursement diagnostic test, SIGFRIED and EEG LI test could be offered by many hospitals and private physicians. Thus more patient would benefit from the significant advantages which these cutting-edge development results provide.

# 9 Indices

## 9.1 Abbreviations

<b>AANC</b>	<b>A</b> ssociation of <b>A</b> merican <b>M</b> edical <b>C</b> ollege
<b>AANS</b>	<b>A</b> merican <b>A</b> ssociation of <b>N</b> eurological <b>S</b> urgeons
<b>ALS</b>	<b>A</b> myotrophic <b>L</b> ateral <b>S</b> clerosis
<b>ANN</b>	<b>A</b> merican <b>A</b> cademy of <b>N</b> eurology
<b>BCI</b>	<b>B</b> rain <b>C</b> omputer Interface
<b>BOLD</b>	<b>B</b> lood <b>O</b> xxygenation <b>L</b> evel <b>D</b> ependent
<b>CBTRUS</b>	<b>C</b> entral <b>B</b> rain <b>T</b> umor <b>R</b> egistry of the <b>U</b> nited <b>S</b> tates
<b>CFR</b>	<b>C</b> ode of <b>F</b> ederal <b>R</b> egulations
<b>CGMP</b>	<b>C</b> urrent <b>G</b> ood <b>M</b> anufacturing <b>P</b> ractice
<b>DMU</b>	<b>D</b> ecision <b>M</b> aking <b>U</b> nit
<b>ECoG</b>	<b>E</b> lectro <b>c</b> orticogram
<b>EEG LI test</b>	<b>E</b> lectro <b>e</b> ncephalogram <b>L</b> ateralization <b>I</b> ndex test
<b>FDA</b>	<b>F</b> ood and <b>D</b> rug <b>A</b> dministration
<b>fMRI</b>	<b>F</b> unctional <b>M</b> agnetic <b>R</b> esonance <b>I</b> maging
<b>IDE</b>	<b>I</b> nvestigational <b>D</b> evice <b>E</b> xemption
<b>ISAP</b>	<b>I</b> ntracarotid <b>S</b> odium <b>A</b> mobarbital <b>P</b> rocedure
<b>ISO</b>	<b>I</b> nternational <b>O</b> rganization for <b>S</b> tandardization
<b>IRB</b>	<b>I</b> nstitutional <b>R</b> eview <b>B</b> oard
<b>PMA</b>	<b>P</b> re <b>M</b> arket <b>A</b> pproval
<b>MEG</b>	<b>M</b> agneto <b>e</b> ncephalography
<b>NAEC</b>	<b>N</b> ational <b>A</b> ssociation of <b>E</b> pilepsy <b>C</b> enters
<b>PET</b>	<b>P</b> ositron <b>E</b> mission <b>T</b> omography
<b>SEER</b>	<b>S</b> urveillance, <b>E</b> pidemiology, and <b>E</b> nd <b>R</b> esults
<b>SIGFRIED</b>	<b>S</b> IGNAL modeling <b>F</b> or <b>R</b> ealtime <b>I</b> dentification and <b>E</b> vent <b>D</b> etection

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# 10 Appendix

## Epilepsy centers

Electrodiagnostic
<ul style="list-style-type: none"> <li>a) 24-hour video-EEG with surface electrodes supplemented with sphenoidal or appropriate additional electrodes. Continuous supervision by EEG technologist or epilepsy staff nurse, supported when appropriate by monitoring technician or automated seizure and interictal activity detection program.</li> <li>b) Intracarotid amobarbital (Wada) testing or mechanism to obtain one</li> <li>c) Intraoperative Electroconvulsive Therapy</li> <li>d) Adequate volume of video-EEG monitoring for seizure classification or localization annually (at least 50 cases)</li> </ul>
Epilepsy surgery
<ul style="list-style-type: none"> <li>a) Emergency or elective neurosurgery, including biopsy and removal and treatment of cerebral complications of epileptic seizures.</li> <li>b) Management of surgical complications.</li> <li>c) Surgical resection of epileptogenic structural lesions with the goal (“straightforward lesionectomy”).</li> <li>d) Standard anterior temporal lobectomy in the presence of mesial temporal</li> <li>e) Experience in resective epilepsy surgery</li> <li>f) Implantation and management of vagus nerve stimulators or other devices.</li> <li>g) If the third level center does not actually perform surgery, it must referral procedures with one or more level 4 surgical centers.</li> </ul>
Imaging
<ul style="list-style-type: none"> <li>a) Magnetic resonance imaging (in 2009, defined as a minimum of 1.5T) with appropriate magnet strength and sequences for the sensitive detection of mesial temporal sclerosis and common epileptogenic lesions.</li> <li>b) Computerized axial tomography</li> <li>c) Cerebral angiography</li> </ul>

Table 9.1: “Third–Level Medical Center for Epilepsy” Gumnit, Walczak and National Association of Epilepsy Centers (2001).

Electrodiagnostic
<ul style="list-style-type: none"> <li>a) 24-hour video-EEG with surface electrodes supplemented with sphenoidal or appropriate additional electrodes. Continuous supervision by EEG technologist or epilepsy staff nurse, supported when appropriate by monitoring technician or automated seizure and interictal activity detection program</li> <li>b) 24 hour video-EEG recording with intracranial electrodes (subdural, epidural or depth electrodes) under continuous supervision and observation as above. Level 4 centers should have an average of at least 6 cases with indwelling or intraoperative electrodes annually averaged over 4 years</li> <li>c) Intracarotid amobarbital (Wada) testing</li> <li>d) Functional cortical mapping by stimulation of subdural electrodes either extraoperatively or intraoperatively.</li> <li>e) Evoked potential recording capable of being used safely with intracranial electrodes.</li> <li>f) Electrocorticography.</li> <li>g) Adequate volume of video-EEG monitoring for seizure classification or localization annually (at least 100 cases).</li> </ul>
Epilepsy surgery
<ul style="list-style-type: none"> <li>a) Emergency or elective neurosurgery, including biopsy and removal of incidental lesions and treatment of cerebral complications of epileptic seizures.</li> <li>b) Management of surgical complications.</li> <li>c) Open and stereotactic biopsy</li> <li>d) Surgical resection of epileptogenic structural lesions with the goal of treating seizures (“lesionectomy”).</li> <li>e) Anterior temporal lobectomy with or without mesial temporal sclerosis.</li> <li>f) Placement of intracranial electrodes.</li> <li>g) Resection of epileptogenic tissue in the absence of structural lesions.</li> <li>h) Implantation and management of the vagus nerve stimulator or other neuromodulatory devices.</li> <li>i) If the center does not offer corpus callosotomy and hemispherectomy, it should establish referral procedures with fourth level centers offering these services.</li> </ul>
Imaging
<ul style="list-style-type: none"> <li>a) Magnetic resonance imaging (in 2009, defined as 1.5T) with appropriate magnet strength and sequences for the sensitive detection of mesial temporal sclerosis and common epileptogenic lesions.</li> <li>b) Computerized axial tomography</li> <li>c) Cerebral angiography.</li> <li>d) Access to one or more of the following either on site or by established arrangement: <ul style="list-style-type: none"> <li>i) interictal positron emission tomography</li> <li>ii) ictal single photon emission computed tomography</li> <li>iii) functional magnetic resonance imaging (fMRI)</li> <li>iv) MEG</li> </ul> </li> </ul>

Table 9.2: “Offered services by a fourth–Level Medical Center for Epilepsy” Gumnit, Walczak and National Association of Epilepsy Centers (2001).