Utrecht Neural Prosthesis (UNP)

A pilot study on controllability of brain signals and application in locked-in patients

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Coordinating investigator/project leader	***Prof. dr. N.F. Ramsey*** ***UMC Utrecht*** ***Dept. Neurosurgery*** ***G03.124*** ***Heidelberglaan 100*** ***3584 CX Utrecht*** ***N.Ramsey@umcutrecht.nl*** ***+31 (0) 88 75 56862***
Principal investigator(s) (in Dutch: hoofdonderzoeker/ uitvoerder) ***<Multicenter research: per site>***	***Prof. dr. N.F. Ramsey*** ***UMC Utrecht*** ***Dept. Neurosurgery*** ***G03.124*** ***Heidelberglaan 100*** ***3584 CX Utrecht*** ***N.Ramsey@umcutrecht.nl*** ***+31 (0) 88 75 56862***
Sponsor (in Dutch: verrichter/opdrachtgever)	***UMC Utrecht***
Subsidising party	***UMC Utrecht***
Independent physician(s)	***Prof. dr. C.J. Kalkman*** ***UMC Utrecht*** ***Dept. Neurosurgery*** ***F06.149*** ***Heidelberglaan 100*** ***3584 CX Utrecht*** ***C.J.Kalkman@umcutrecht.nl*** ***+31 (0) 88 75 59677***
Laboratory sites <*if applicable*>	***N.A.***
Pharmacy <*if applicable*>	***N.A.***

PROTOCOL SIGNATURE SHEET

Name	Signature	Date
Head of Department: ***Prof. dr. P. Robe***		23.5.24
[Coordinating Investigator/Project leader/Principal Investigator]: ***Prof. dr. N.F. Ramsey***		17-05-2024

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	**ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, ABR = Algemene Beoordeling en Registratie)**
AE	**Adverse Event**
AR	**Adverse Reaction**
AT	**Assistive Technology**
BCI	**Brain Computer Interface**
CA	**Competent Authority**
CCMO	**Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek**
CV	**Curriculum Vitae**
DSMB	**Data Safety Monitoring Board**
EU	**European Union**
EudraCT	**European drug regulatory affairs Clinical Trials**
GCP	**Good Clinical Practice**
IB	**Investigator's Brochure**
IC	**Informed Consent**
IMP	**Investigational Medicinal Product**
IMPD	**Investigational Medicinal Product Dossier**
METC	**Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)**
(S)AE	**(Serious) Adverse Event**
SPC	**Summary of Product Characteristics (in Dutch: officiële productinfomatie IB1-tekst)**
Sponsor	**The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.**
SUSAR	**Suspected Unexpected Serious Adverse Reaction**
Wbp	**Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens)**
WMO	**Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

SUMMARY

Rationale

In this pilot study we will provide locked-in people with a new means of communication which has not been possible up to now. For the first time, we will test whether we can record and decode neural signals obtained directly from the brain, for control over a computer. The target population is severely paralyzed, due to trauma, brainstem stroke, neuromotor disease or another cause, and has no means of communication other than for instance eye blinks. This condition is called the locked-in syndrome. For these patients there is no technique available to allow them to communicate unaided. We have developed a brain-computer interface (BCI) system that can read activity directly from the brain, and can convert the activity to a digital switch. The system, called the Utrecht Neural Prosthesis (UNP), consists of an implantable amplifier for electrical brain signals, a set of electrodes positioned on the surface of the brain and a wireless receiver (constituting the 'Medtronic System'). This was recently developed by Medtronic, a company specialized in medical implantable devices such as Deep Brain Stimulators and pacemakers among others, and has been tested for the current application by our group at the UMC. A dedicated computer will convert the signals to electrical pulses for standard Assistive Technology (AT) devices (UMC Brain Interpreter, developed at the UMC with the Medical Technology Dept). The amplifier and electrodes are fully implanted and signal is transmitted wirelessly through the skin. Crucial elements of the UNP are exact positioning of electrodes on the cortex (after accurate localization of two brain functions and associated regions), and the specific features extracted from the complex brain signals. The UNP can in principle enable the patient to engage in any activity that is offered by commercial Assistive Technology companies that can be performed with switch signals, for instance operating home apparatus such as lights, tv, curtains etcetera, or writing text for emailing. Since we do not yet know how proficient participants can operate the BCI system, the ability to switch home devices on or off may not be safe. Therefore for the current pilot study we will initially limit use of the BCI system to making selections on a computer screen, and to writing text. In the course of the study (once patients have reached a certain level of proficiency), the possibility of environmental control (e.g. tv, lights) may be made available to the patient. Decisions about this will be made on an individual basis. Most importantly, we aim to achieve unsupervised function of the BCI, meaning that the patient will be able to use it at home without the aid of researchers or other experts (but with minimal caregiver assistance). The device, consisting of amplifier, electrodes and the wires connecting them to each other, will be implanted in 5 patients. Research will be conducted for 12 months after implant and may be extended if the participant chooses to continue participation.

Objective

The main goal is to achieve a means of communication solely based on brain signals for locked-in patients. Success will constitute a significant advance in the field of BCI and of severe paralysis because it will be the first system that allows for unsupervised operation. For this, we need to investigate feasibility in the current pilot study. Several objectives are

defined, all representing performance of the BCI system in real life. The primary objective is to achieve communication via our BCI system in locked-in patients, as measured in terms of writing a sentence on a computer without help from a member of the BCI research team (unsupervised use). Two secondary objectives are defined being a) Improve Quality of Life and user satisfaction with the BCI system, and b) Assess experimental parameters for a larger clinical study.

Study design

This study is an interventional study, lasting 5 years. It is a pilot study preparing the ground for a larger clinical trial, and has an *adaptive trial design*, where we allow for modifications to be made concurrently (e.g. in/exclusion criteria) or prospectively (e.g. discontinuation following interim evaluation, modification of end-of-study date), in communication with DSMB and METC committee (Thabane et al., 2010).

Study population

Five patients of age 18-75 years, with severe paralysis and only an aided means of communication (e.g. eye blinks) or no means of communication.

Intervention (if applicable)

A device will be implanted, to detect and analyze brain signals. After the surgical implant procedure, feedback is given of brain activity via a visual display. Successful control over the brain signal will improve a patient's wellbeing since it offers a means of communicating. Failure to control the signal will induce disappointment. No detrimental effects on physical or mental health are to be expected.

Main study parameters/endpoints

Primary endpoint is proficiency of use of the BCI system. For this we recognize three levels of proficiency: First, the level of proficiency described as the primary objective, being *unsupervised BCI performance* (with the caregiver enabling/disabling AT device control), with the criterion that the patient is able to write text without help (using a formal test). Second, we define an intermediate (lower) level of proficiency, which represents a level equivalent to that of the communication channel that the patient had before participation, being *supervised BCI performance*, where the patient is able to generate click commands with at least 80 % correct, with the help of a BCI researcher and/or caregiver (using a formal test). A third level of control is defined as *independent BCI performance*, where the patient is capable of enabling / disabling AT device by himself. This requires the highest level of control achievable.

Thus, the three levels, in order of proficiency are:
1) Supervised use, dependent on continuous assistance for communication
2) Unsupervised use, ability to communicate without assistance for limited periods
3) Independent use, ability to communicate without assistance at any time of day or night.
Note that level 2 is the primary objective of the study.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness

The research is fully directed at the patient population participating in the study. The participating patients are likely to experience benefit from participation in terms of acquiring a new means of communication for the duration of the study. If the study succeeds in its objectives, it can provide patients with the means to engage in interaction with others and with their environment without the help of others, and at any time. This degree of autonomy is not available in any other way for these patients.

The research is at risk of failing to provide communication, because there are no data from chronic implants yet that would allow us to estimate performance of the BCI system in real life. Worst case scenario we need to explant the device due to medical complications associated with the surgery. The risk of medical complication is the same as for deep-brain stimulators (standard clinical treatment for Parkinson's disease). The burden consists of recovery from the implant, and from participation in multiple test and calibration sessions aimed at optimizing BCI performance. The benefit ranges from none (failure to decode brain signals) to large (new means of communicating with others).

1. INTRODUCTION AND RATIONALE

Background and state of affairs

The ability to generate movements is indispensable for expression of oneself. Without muscle control one cannot convey any wish, intention or emotion nor interact with the environment. We generally take this ability for granted but what if one has full mental capacities but no muscle control? One is then effectively 'locked-in' (Locked-in Syndrome, LIS), a gruesome condition with complete dependence on others for survival and virtually no means of communication or even of expressing an emotion such as pain, (dis-) approval or sadness. We currently cannot offer locked-in patients any restoration. Reading imagined sensorimotor acts directly from the brain (brain-computer interfacing, BCI) has long been regarded the way towards restoring communication (Wolpaw et al., 2004) but progress has been painstakingly slow, in part due to limitations that the skull imposes on scalp EEG, the prevailing technique of the field.

The only EEG-based BCI technique with which reasonable results were obtained in paralyzed users, is the P300 technique where brain signals reveal which character in a matrix on a computer screen the user is looking at. This technique, which requires flashing of the character on the screen, was developed more than 25 years ago (Farwell & Donchin, 1988) and developments have been exhausted. At this time, a very select few paralyzed people achieve reasonable to good performance with P300 (Mak et al. 2012, Sellers et al. 2010). However, except for one case (Sellers et al. 2010) there are no reports of effectiveness of EEG BCI systems in the home situation, where researchers are not present to ensure proper operation of the system. A first clinical trial is being conducted (started in 2006, Vaughan et al. 2006), but results have not been published yet. Informal communication with the lead PI reveals that the P300-BCI system works fairly well for a subset of users, and that reliability is one of the important limitations for at least part of the tested patients (Jon Wolpaw, personal communication). For locked-in patients EEG-BCI performance is lower than for less severely paralyzed users (Kuebler et al. 2008),

Reliability is the measure for performance of the BCI system in terms of error rate. Good reliability is achieved when the system acts when the user wants it to, and does not act when the user does not want it to. The most important limiting factor in achieving high reliability is the signal itself. Amplifiers and decoding algorithms have been the topic of intensive research for decades, and further improvements are only marginal. Still, EEG BCI performance is not impressive: in controlled settings (with engineers/experts present) most healthy people obtain 70-90 % hit rates (Guger et al. 2009) and patients (eg ALS, Mak et al. 2012) obtain rates in the order of 50-70 % (here either patient performs well or very poorly). Performance is not only affected by quality of the brain signal (which varies greatly across subjects), but also by mental state of the user such as fatigue and motivation, and in the case of paralyzed users, the expertise and willingness of the caregiver. The EEG-BCI system requires daily positioning of a cap with electrodes which still require abrasive gel for adequate conductivity. Patients generally do not appreciate the skin irritation caused by

frequent use of the gel (Vaughan et al. 2012), which is one of the reasons (in addition to reliability) why people do not want to use EEG-BCI (Roadmap FBNCI). If reliability and controllability are too low, users will abandon the application, a well-known phenomenon in the field of assistive technologies (Phillips et al. 1993). For daily use fitting the cap can result in suboptimal signal recording (misplacement, insufficient gel application), which further threatens usability (Kleih et al. 2011). Much is expected from development of dry and water-based electrodes, both of which should be more comfortable, but after more than 10 years of research, these have not been able to provide the same signal quality as gel-electrodes, thus leading to lower performance (Roadmap FBNCI)

Progress in attempts to improve reliability of EEG-BCI systems and use by paralyzed people is generally discouraging. In an important document created by all the lead scientists in the European field of BCI, compiled for the EC in the FP7-ICT program (FBNCI roadmap for BCI research in Horizon 2020, www.future-bnci.org), the current state of the art and the improvements that can be expected for the next decade are described. It concludes that reliability is not favorable for home use in paralyzed users, and that most of the recommended development concerns user friendliness of the various components of BCI systems. It is striking that no major improvements are expected in the quality of brain decoding or reliability of EEG-BCI systems. The report recommends continuation of the research as it has been performed for decades, with emphasis on improving essentially cosmetic and comfort issues. This rather disappointing perspective agrees with the lack of reports on home use, and with the fact that the key element of all EEG BCI systems, namely signal quality (signal to noise ratio), is fundamentally low due to skull and scalp. It also agrees with reviews published by lead groups in EEG-BCI research, where the need to improve reliability continues to remain one of the key issues (Shih et al. 2012, Vaughan et al. 2012, Fazel-Rezai et al. 2012). Authors do increasingly recommend pre selection of patients to improve results, because many people are not able to use EEG-BCI systems at all or well enough (Vaughan et al. 2012, Mak et al. 2012).

In summary, careful examination of the literature (confirmed in personal communication with lead researchers on EEG-BCI) shows that current EEG-BCI systems have little to offer severely paralyzed people, because of insufficient reliability. Significant improvement in reliability is not to be expected given that all technical elements are currently of very high quality (amplifiers, interface software, decoding algorithms). It is not technology that limits performance, but the mediocre quality of the brain signal recorded from the scalp.

The most fundamental and in our view the most important limitation of EEG-BCI is that the system does not provide any assistance when it is not attached to the patient. The few paralyzed people who use an EEG-BCI system on a regular basis in the home (eg Sellers et al. 2010) do so for a few hours at a time. The rest of the time, locked in users have no means of initiating communication. Someone who can generate a sound can ask for attention. Someone who is locked in cannot and has to wait until the caregiver initiates contact. An effective BCI system has to overcome this severe limitation if the goal is to improve the life of

locked-in patients. Only an implant that is permanently operational can offer such an improvement.

Intracranial solutions

Signals recorded *directly* from the brain are significantly more detailed than scalp EEG since electrodes record from their immediate, neuronal, environment (Jacobs and Kahana, 2010). Signal to noise ratio is impressive, allowing for detection of even very local changes in brain activity (Vansteensel et al., 2010; Ramsey et al., 2006). Most in the BCI field will agree that signals recorded directly from the brain are of a much better quality than scalp-EEG. In one recent clinical pilot in the USA, researchers succeeded in decoding imagined movements in paralyzed people with an array of needle electrodes implanted in the cortex (Hochberg et al., 2006, 2012), enabling them to move a cursor across a computer screen. This pilot showed that direct brain signals could be decoded in all 5 patients included. An important drawback is the insertion into the cortex which may induce gliosis which leads to loss of signal after months or years. A new approach is one where electrodes consist of small discs that lie on top of the cortex, measuring from several mm of neuronal tissue without damaging it (Leuthardt et al., 2004). We at the UMC have been conducting research on these electrodes and their potential for BCI, which is described below.

Our BCI system requires surgery. For people who need BCI the most, those who are locked-in, surgery is not necessarily an issue. Neural implants are already widely used, such as cochlear implants, deep-brain stimulators and spinal cord stimulators (tens-hundreds of thousands). Implanting electrodes for BCI in fact carries less risk than deep-brain stimulators with electrodes positioned deep in the brain, since BCI electrodes remain at the surface. The limiting factor in intracranial BCI is our understanding of brain signals at the level of detail that is obtainable with surface electrodes. Unlike EEG, we can only obtain brain signals from patients who need electrodes for other purposes, such as certain patients with epilepsy. When the source of seizures cannot be determined with EEG or MRI, and the patient does not respond to medication, they are eligible for an electrode grid implant procedure, where about 120 electrodes are implanted on the surface of the cortex, under the dura. This recording technique is called electrocorticography (ECoG). After implant, the electrodes are attached to a clinical EEG system and the patient is monitored (signals recorded) for 7 days. While the clinic awaits a natural seizure (the start of which can be traced to the source in the recorded brain signals) patients can participate in BCI research, as they have for the last 4 years at the UMCU. We have extensively tested ways to record and decode brain activity from these study participants and have developed a procedure for selecting specific brain regions for BCI. Moreover, an implant company (Medtronic Inc) has developed an implantable amplifier with electrodes and leads, which we have tested for potential application for BCI. The results are highly promising and with what we have investigated and developed, we are ready to start implanting our BCI system in locked-in people. If we succeed in obtaining our goals, these patients will obtain a new means of communication, which they can engage whenever they want to, that cannot be obtained in any other way. It will be one or more simple but highly reliable brain switches, where the patient can generate

a command by either counting backwards, or imagining/attempting making hand movements. A single switch allows for control of communication software in ‘scanning’ mode, where the user waits for the automatic sequential highlighting of different letters or icons and produces a brain-switch to select the desired item when it is highlighted. With multiple switches, the speed of communication can conceptually be increased. For instance, with two different intentions, rows and columns can be controlled with their own switch, which allows self-paced scanning. If four different intentions can be identified and distinguished (e.g. 4 different hand/finger movements for ‘top’, ’bottom’, ’left’, ’right’), one can conceivably proceed through 4-choice menus and thus rapidly navigate through customized communication software.

Preparatory research

We have conducted as much of the research as possible in epilepsy patients but at this point further research requires participation of people in the target population. BCI control over a cursor was successful in most of our experiments with epilepsy patients, encouraging us to make the current step of implanting a BCI system in 5 locked-in patients. Important knowledge is now needed for achieving a functioning BCI system. We expect the system to be functional within a few weeks but since we have no means of investigating this without chronically implanting systems, we cannot be absolutely sure. So, this study involves implanting a BCI system that has been tested as much as possible, and which has been successful in our epileptic study participants, and extensive testing and improving it over the course of one year at the home of the patient. We have all the procedures for chronic recording of brain signals, for finding the best decoding algorithms, for evaluating performance improvements and learning effects, and for evaluating patient satisfaction with the system, in place.

In recent years we investigated several important elements of the ECoG-BCI system. The best electrode target region for BCI proved to be the dorsolateral prefrontal cortex, which is controlled by mental calculation (counting backwards in the head leads to a highly reliable increase in signal) (Ramsey et al., 2006, Vansteensel et al., 2010). Although this region and function has yielded by far the most robust BCI signal in our studies, a backup region will also be targeted. This is the precentral gyrus which activates when people imagine making movements (Hermes et al., 2011b). These regions can be accurately identified with functional MRI before the implant procedure (Vansteensel et al., 2010, Hermes et al., 2011a). Decoding of the signal is quite high in all subjects tested (Vansteensel et al., 2010), and with a specially developed algorithm, the number of ‘false positives’ (i.e. when the system generates an unintended ‘yes’ signal) can be reduced to a very small number (Torres Valderrama et al., 2012). Electrodes need to be positioned under the dura and not on top of blood vessels, since the brain signal is attenuated by a factor of 10 and 2 respectively (Torres et al., 2010; Bleichner et al., 2011). The optimal signal features for BCI is the power in the gamma range since it yields very high decoding performance and low false positive rates (Vansteensel et al., 2010, Torres Valderrama et al., 2012).

In summary, we have developed an implantable BCI solution for locked-in people, with the help of epilepsy patients with implanted electrode grids. At this point all the research that could be conducted for the BCI solution has been performed. Moving the technology to the target population now requires testing in several locked-in people. The study is designed as a pilot study to obtain proof of concept of unsupervised intracranial BCI. The study is set up in such a way that it will provide evidence in favour of, or against, conducting a larger clinical trial. The data collected in this pilot study can be included in the larger study.

We wish to stress that we aware of the fact that implanting hardware close to the brain may be considered as a form of enhancement. Especially if our study will be successful, ethical questions may arise about aspects of future research and use. We expect that the coming years will come with significant discussions and insight in this area, which will be extremely important for future decisions. The experience we gain from the current study will allow us to form opinions in these important matters and to play a role in the public debate.

Parameters to be investigated

To achieve our objectives we will investigate and improve parameters that affect performance. Key questions we will address are:
1) Are the brain functions and associated cortical foci we have selected adequate for unsupervised BCI? Here we address stability of classification of commands (accuracy) over time and frequency of false detection of a 'yes command' (false positive rate)

2) What factors affect a patient's control over the system? Here we evaluate beneficial factors such as operant conditioning of brain activity, type of algorithm for decoding, signal features for decoding, methods of online adaptation to adjust for signal fluctuations. We also evaluate significance of potentially disruptive factors such as habituation of brain responses, patient fatigue, and impact of high false positive rates on patient mood.

3) What determines improvement in patient satisfaction, perceived added value to daily life and quality of life?

4) Which variables are of interest for assessment of BCI functionality of the system in a larger clinical trial?

Key parameters based on prior research

Extensive work performed in the last 4 years in our lab has focused on critical parameters for intracranial BCI. Key is to obtain the highest performance during a supervised task, to have a very low rate of false positives (unintended 'yes' commands) and to achieve control with a minimal training period. The critical parameters are: where to place electrodes (brain function and region), what signal features to utilize and what to use as a reference for the signal. Each will be presented separately.

Position of electrodes

To maximize chances of success we target two functions and corresponding regions of the brain. First, the motor system, which is the most widely used for EEG-BCI because a) the signal is strong enough to detect from the scalp, and b) imagining movements generates a signal that is similar to one generated by actual movement. It is thought that such activity originates from the primary motor cortex (M1). It is not clear why M1 would become active, but the phenomenon is utilized nonetheless for EEG BCI. There are, however, some issues of concern. First, and highly relevant for identifying a cortical target for implanting electrodes, we have shown with functional MRI in healthy volunteers that it is not the primary motor cortex that is activated, but the regions immediately anterior (premotor cortex) and posterior (postcentral gyrus) (Hermes et al., 2011b). On EEG this may look similar to motor execution activity since these regions are fairly close to each other (2-3 cm) and may not be separable in scalp EEG (and are then seen as one region, located in-between). The two regions are associated with planning of motor acts, and with sensory feedback respectively. This finding has been replicated by a well-known EEG BCI group (Halder et al., 2011). Thus, although success with motor imagery for BCI is frequently reported for scalp EEG, the actual regions involved may not be M1. Moreover, such higher-order regions are likely to also activate when observing other people's movements (Halder et al., 2011), potentially leading to high rates of false positives in BCI application. Second, there are indications that efferent motor nerves play an important role in the ability to imagine movements, and that paralyzed people consequently have problems with imagery (Decety et al., 1990, Conson et al., 2008). Indeed attempts at detecting imagery-related brain activity is significantly less successful than in healthy volunteers (Stanton et al., 2007 and unpublished reports from EU consortia TOBI and BrainAble). On the other hand, there is evidence that paralyzed people can attempt to make movements, and that this may induce activation of the primary motor cortex (Hotz-Boendermakers et al., 2008). In the present project we will therefore target both *pre*motor and motor regions for BCI.

The second target region is one that has shown excellent properties for BCI. It is the anterior dorsolateral prefrontal cortex that serves Cognitive Control function. This region is activated by consciously processing internal information, such as counting backwards, for instance in steps of 7 (203 > 196 > 189 etc), and as such is fully independent from external stimulation. This region works well in every epilepsy patient who had electrodes placed there as evidenced by an extensive study we conducted recently (Vansteensel et al., 2010, Ramsey et al., 2006). Moreover, false positive rate can be kept quite low (Torres Valderrama et al., 2012).

Placement of electrodes requires presurgical localization of functions because the exact location of WM and motor regions varies across individuals. For this we will use functional MRI on a 3 Tesla scanner of the UMC. For the last 10 years we have developed and refined a scan technique that has proven to be an accurate function localizer: PRESTO fMRI. This technique is now routinely used to map brain functions for patients planned for neurosurgery, to spare motor, language and cognitive control function (Rutten et al., 1999; Rutten et al., 2002; Kho et al., 2007; Neggers et al., 2008; Hermes et al., 2011a). We will implant four

strips with 4 electrodes each to obtain optimal coverage of targeted brain functions. Two strips will be connected to the device, and optimal configurations are chosen for optimal BCI signal. To identify the best 2 strips we will perform the implant procedure in two steps: first, the four electrode strips are implanted based on fMRI scans, using neuronavigation at the operating room (standard equipment). The wires are connected under the skin to extension leads that exit the body at the abdomen. These are then connected to the clinical ECoG system for 2 days. In this time all electrodes are recorded and tests are performed to determine the optimal strips and configurations. Once this has been determined, the extension leads are removed, the device is implanted on the chest (standard position for deep-brain stimulators) and the leads are finally connected. The two unused strips remain in place, and their leads are capped (to protect the contacts).

Signal features

Signals can be decomposed into frequency bands using Fourier transform or equivalent techniques. The amplitude of each frequency can be tracked over time. For EEG-BCI the lower frequencies can be detected the best, notably in the range of 8-24 Hz. Higher frequencies are detectable with intracranial electrodes, up to several hundred Hz (Gaona et al., 2011). We have extensively researched the most useful signal features for BCI, and have found that power in the range of 50-100 Hz ('gamma power') is highly correlated with self-generated brain activity. Lower frequencies also correlate with function but are less regionally specific and, as a consequence, also change power in response to other brain functions. Lower frequencies thus produce more false positive events (erroneously detected 'yes' events) than the gamma range. This was formally tested and reported in Torres Valderrama et al., 2012. Foci exhibiting gamma power changes correlate well with fMRI signal changes, the implication of which is that we can accurately localize the brain functions of interest (Vansteensel et al., 2010; Hermes et al., 2011a).

Electrode reference

In most of the experiments with epilepsy patients, we used the average signal over all electrodes as the reference for signal from individual electrodes. For this the mean signal was subtracted from the signal of each electrode, which is effective for removing signal artefacts. This is standard procedure for ECoG research in general. For our current purpose, where we can only measure from 4 electrodes, this technique does not work because the signal of interest would likely be eliminated (too few electrodes for an average), The device does allow for referencing single electrodes, meaning that we can measure the difference between two electrodes. We have investigated the possibility of obtaining adequate BCI signal from two closely positioned electrodes and found that a good BCI signal was obtained if both electrodes measure from brain tissue that is involved in the targeted brain function. Moreover, exact foci can be found with fMRI given that fMRI foci exhibit gamma power changes. Thus, for the present study we will position the four strips along highest activity foci localized with fMRI and projected along the surface of the brain.

In summary, this protocol describes a pilot study involving 5 locked-in participants, and surgical implant of a medical device that amplifies brain signals and transmits signals wirelessly through the skin. External equipment converts the signal into ‘clicks’ in computer programs that enable the user to express choices. In as much as possible, the parameters that are critical for making the BCI system work, have been investigated in epilepsy patients who received intracranial electrodes for diagnostic purposes. The system is considered likely to function as expected but this pilot study is necessary to determine the impact of chronic use on parameter selection. Positive results will form the basis for a clinical trial of the system, providing optimal parameters and appropriate evaluation indices.

2. OBJECTIVES

Primary Objective

To achieve communication via our BCI system in locked-in patients, as measured in terms of writing a sentence on a computer without help from a member of the BCI research team (*unsupervised use*). The research aims to evaluate performance of the BCI system at the start of implantation, and to then optimize performance. Development and preliminary testing of the hardware has been completed before start of this protocol. The timeframe is dependent on the progression of BCI training and the patient's condition. Training and measuring visits are initially scheduled maximally twice a week, and every two or six few weeks in later stages (see Section 8.3.9 and 15.4).

Secondary Objective(s)

1. To improve quality of life and user satisfaction with our BCI system. This will be measured with standardized questionnaires and pattern of unsupervised use. Indices of evaluation will be determined for use in a larger clinical trial, based on relationships between initial measures of performance (e.g. % correct, speed, false positive rates etc) and user satisfaction and quality of life. The timeframe is dependent on the progression of BCI training and the patient's condition. Training and measuring visits are initially scheduled maximally twice a week, and every two or six few weeks in later stages (see Section 8.3.9 and 15.4).

2. Assess experimental parameters for a larger clinical study, including decoding algorithms, sample size, augmenting and prohibitive factors affecting BCI performance, factors affecting use of the system and indices of evaluation. This can only be investigated with chronically implanted systems, hence the present pilot study. Timeframe: all data collected during the visits of the research team to the patient can be used to assess these parameters.

3. STUDY DESIGN

3.1 Design

This study is a single center interventional pilot study, lasting 5 years. The population consists of five patients of age 18–75 with severe paralysis. It is a pilot study preparing the ground for a larger clinical trial, and has an *adaptive trial design*, where we allow for modifications to be made concurrently (e.g. in/exclusion criteria) or prospectively (e.g. discontinuation following interim evaluation, modification of end-of-study date), in communication with DSMB and METC committee (Thabane et al., 2010). For inclusion, patients need to possess at least one rudimentary form of communication (see inclusion / exclusion criteria Section 4 for more details). Completely locked-in patients may be included, if there is clear indication that they understand the protocol and the risks and want to participate, and if their legal guardian agrees to (and signs for) their participation. Patients of the target population are typically no longer in medical treatment after their condition is stabilized, and may live at home or in a care center. Since they may therefore be difficult to find and reach, recruitment will be performed in various ways (see Section 4.1 for details).Patients or their caregivers can contact the research team directly, or the research team can contact the caregivers after they have given permission for this to their specialist. Patients will be visited multiple times by the research team, to inform them about the details of the study, to obtain informed consent, to verify the physical and mental abilities of the patient to continue with the procedure and to practice tasks. In addition, an EEG measurement session will be conducted. Results of these EEG recordings will provide information about the neuro-electrical signal features in the low-frequency band (high-frequency band changes cannot be measured reliably with EEG), which may be useful to address secondary objective 2. Notably, the EEG measurements may also take place some time after the electrodes and the device were implanted. See Section 3.2 for a time line and the sections mentioned therein for details.

When a patient is found to be sufficiently healthy for surgery (and meets inclusion criteria), he will be admitted to the UMC for 7-10 days. After standard medical presurgical checks, the patient will undergo an fMRI scan in order to prelocalize brain regions involved in motor imagery/attempt and executive control (Figure 1A). For each patient, it will be determined whether the fMRI activation patterns of motor imagery/attempt and executive control are usable (based on magnitude of activation an anatomical location), and the regions that are the most promising for successful BCI control will be selected. When the exact coordinates are determined, the patient undergoes surgery for implantation of the electrode strips (4 strips, each with 4 electrodes, Figure 1B), using the neuronavigator (clinical Stealth system) and 3D surface renderings of the fMRI activation patterns. After implant of the electrodes, a series of tests is conducted to find the optimal electrode pairs. Once those are determined, a second surgical procedure is performed to implant the device and connect the optimal electrodes to the device (Figure 1C). After recovery the patient is discharged and training with the BCI system commences according to a standard schedule.

The BCI system will remain operational during participation of the study. Twelve months after implant, the participant (or legal guardian) is asked whether he or she wants to continue participation or wants to end participation. If the participant (or legal guardian) chooses to continue, the question about continuation is asked every year until the end of the study. After end of participation, in consultation with the neurosurgeon, a careful choice will be made about the (dis)continuation of use of the device, and the explantation of (parts of) the implanted components.

Notably, as of 2018, this research is funded by a new grant, and focuses more on the detailed organization of the sensorimotor cortex to accomplish faster communication using the BCI. This ethics protocol now also allows the inclusion of people previously implanted with ECoG electrodes and Activa PC+S. For these people, some aspects of the study (e.g. electrode implantation surgery) are not relevant. In sections 4, 8 and 11, these items are marked with '* Because electrodes are already in place, imaging, electrode placement surgery and strip selection procedures are not relevant for new participants with existing implant'. To avoid confusion, the other sections are not marked.

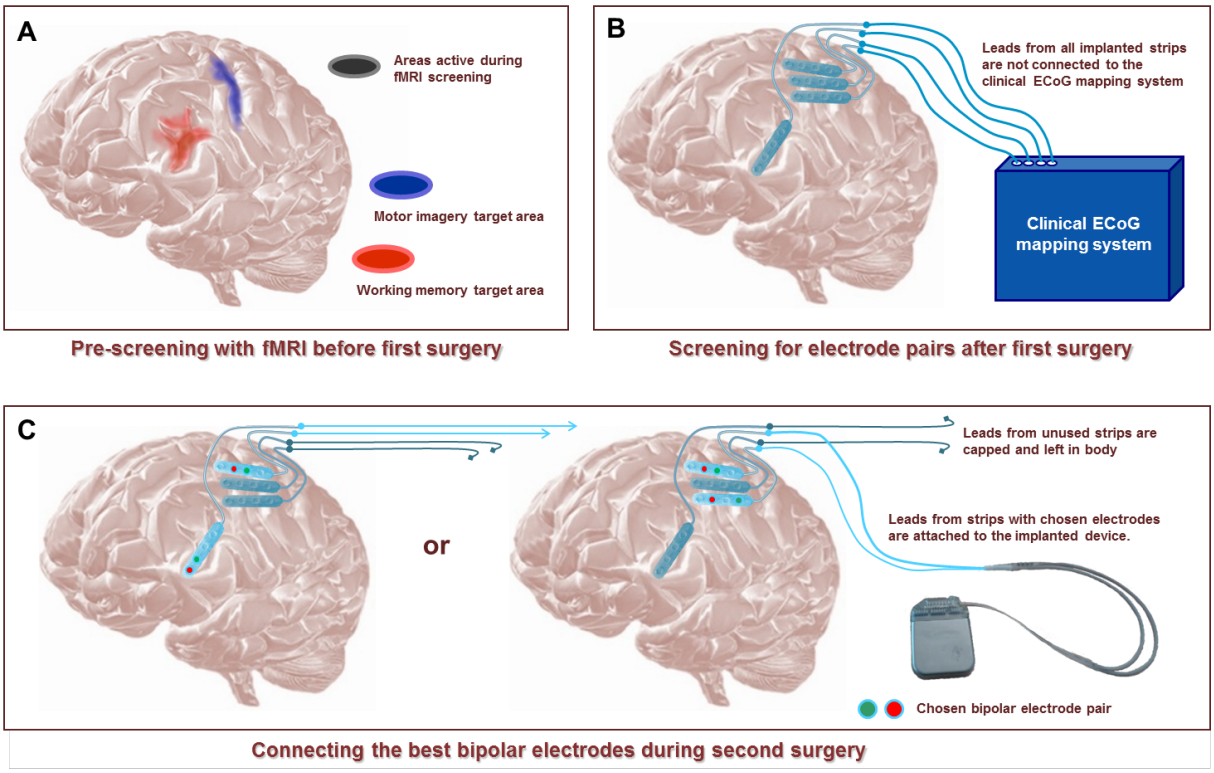

Figure 1, A) Choice of electrode implantation sites using fMRI activation patterns, B) Implantation of 4 electrode strips during the first surgery, C) Connection of the two optimal electrode strips to the Activa PC+S during the second surgery. Depending on the results of tests between surgeries two strips over the motor cortex will be connected, or one strip over motor cortex and one over DLPFC.

3.2 Time Line

This timeline is indicative: if the patient or hospital planning requires more or less time than planned then the total timeline will be adjusted accordingly. In addition, if a certain test, action or task cannot be performed (properly) at the indicated time point (due to e.g. the condition of the patient), it will be repeated on another occasion, or rescheduled to a more appropriate time point.

Week -7	Patient is interested in study
Week -6	Telephone contact with caretakers of patient to verify interest in study and to check main inclusion/exclusion criteria (Section 4.2; Section 4.3; Section 11.2; Section F1.1; Section F1.2)
Week -5	If the patient meets main inclusion/exclusion criteria: Visit by research team: Explanation of the study and verification of communication channel of the patient (Section 11.2; Section F1.3; Section E1.1).
Week -5 to -3	Time to consider participation. During this time further communication verification tests can be held when there is doubt about the communication skills of the patient.
Week -3	Telephone contact with caretakers to verify interest of the patient to join the study
Week -3	If the patient is interested: Visit by research team and neurosurgeon: Second explanation of the study, check of understanding of the study (Section 11.2; Section F1.4)
During week -3	Several days time to consider participation, followed by telephone contact with caretakers to verify continuing interest of the patient to join the study
Week -3	If the patient is still interested: Visit by the research team: Verification of communication channel of patient, check of understanding of the study, and informed consent procedure (Section 11.2; Section F1.3; Section F1.4; Section E2). If the patient (or legal guardian) has given informed consent: Actual study starts.
Week -3 – 0	EEG measurement session. Notably, these measurements may also take place at a suitable moment after implantation of the electrodes and the device.
Week -2	Visit by neuropsychologist and a member of the research team: Presurgical psychological and neuropsychological testing (depression, cognitive functioning, quality of life, importance of device aspects; Section 8.3.1; Section F1.5; Section F1.6; Section F1.8A). This visit does not take place if participants have an unreliable communication channel. Patient receives written information about fMRI tasks to perform in scanner (Section 8.3.3; Section E1.2).
Week -1	Visit by research team for practice of fMRI tasks, and by anesthesiologist to check for surgery eligibility (Section 8.3.2)
Week 0	Transportation to hospital with transport suitable for patient. Admission to hospital (Zorglijn FNO).

For patients who live abroad, the appointment with the neurosurgeon may take place via a video call. The subsequent informed consent procedure, EEG recording, neuropsychological evaluation (if applicable), fMRI scan and anesthesiological evaluation will take place at the UMCU. Scheduling of these procedures will be done in consultation with the patient (or legal guardian) and may involve a single multi-day visit to the Netherlands (i.e. stay at a hotel) or several separate visits.

Schedule in hospital from moment of arrival

Day 1	Presurgical consult with an anesthesiologist to estimate general health (fitness for surgery) (Section 8.3.2) Pre-operative clinical neurological examination by a neurologist (Section 8.3.2) fMRI scan (Section 8.3.3). Prior to the fMRI scan MRI compatibility may be checked with X-ray photos. Notably, if the burden for the patient is considered acceptable by the patient and the research team, the fMRI scan may be scheduled before admission to the hospital. In that case, at Day 1 of admission, a neuronavigation marker MRI or CT scan will have to be performed.
Day 2	fMRI analysis and evaluation, decision about location of electrode implantation (Section 8.3.3)
Day 3	Implant surgery (Section 8.3.6; Section 8.3.7)
Day 4&5	CT scan, recovery and tests to determine optimal electrode pairs for BCI use (Section 8.3.7)
Day 6	Connection surgery (Section 8.3.6)
Day 7	Post-operative clinical neurological examination by a neurologist (Section 8.3.2). Until release (probably around day 9-10): Recovery, post-implantation testing and BCI training (Section 8.3.9).

Subsequently, patients will return home with suitable transport, at which point the last phase of the study begins. During this period, the research team will visit the patient on a regular basis for BCI training, help in BCI use at home and data collection for research (Section 8.3.8; Section 8.3.9; Section 8.3.10; Section 8.3.11; Section 8.3.12; Section 15.4; Section F1.6; Section F1.7; Section F1.8; Section F1.10). During the study it may be helpful to make extra CT scans or EEG measurements, for instance in the case of signal deterioration or decline of BCI performance. This will be discussed with the participant and their medical condition will be taken into consideration. In the case of an extra CT scan, a hospital visit will be scheduled. An EEG measurement can be performed at the participant's home or at the UMC Utrecht, depending on the wishes of the participant. The results of these additional measurements may be compared with the results of the presurgical measurements. These comparisons may help understanding the cause of signal changes and/or the influence of disease progression on BCI performance.

For patients living abroad, surgery and perisurgical procedures will take place at the UMCU. BCI training, BCI home use and postsurgical data collection will take place at the home of the participant under local ethical approval.

4. STUDY POPULATION

4.1 Population (base)

The study population consists of patients of age 18–75 years who are in a locked-in state, i.e. patients with severe paralysis and communication problems as a result of that. The severity of the disability is essential for inclusion, not the cause (could be stroke, high spinal cord lesion, neuromuscular disease etc). Only patients in a medically stable condition will be considered. The prevalence of patients in this condition is unknown and is probably low. These patients are typically no longer in medical treatment after their condition is stabilized, and may live at home or in a care center. They are therefore difficult to find and reach (this is the reason there are no prevalence and incidence data available).Therefore, an active recruitment program has been designed (see Section 11.2.1).

Five patients will be included in this pilot study (male or female). Inclusion requirements include mental capacities intact, stable psychological condition, and good medical health. Notably, also people who already have two electrode strips over the sensorimotor cortex and an implanted Activa PC+S device in place may be included. More detailed criteria are described below.

4.2 Inclusion criteria

1) Age 18 – 75
2) Locked-in status (i.e. severely paralyzed with communication problems)
- in case of trauma or stroke: at least 1 year after the event
- in case of a neuromuscular disease: slow progression allowed
4) Mentally and physically capable of giving informed consent. If at the time of the informed consent procedure (details in 11.2.2) the patient is not capable to unequivocally communicate consent, earlier expressions of the wish to participate after the patient was given information on the study will suffice.
5) Lives in or close to the Netherlands
6) MR compatible∗
- able to lie flat in the scanner
- no metal objects in or attached to the body
- no claustrophobia
7) Visus (largely) intact
8) Cognition intact (IQ>80)
- In the case of unreliable communication at the time of inclusion, tests of cognitive functioning will not be conducted and results of fMRI analysis will inform the neuropsychologist about the patient's cognitive ability to understand and follow instructions.
9) Compatible with implantation procedure

- good respiratory function or stable respiratory situation using ventilation assistance

4.3 Exclusion criteria

1) Strong and frequent spasms
2) Vital indication for blood thinners
3) Current brain tumor or history of tumor resection
4) Quick medical or neurological deterioration
5) Patients who are considered legally incapable (and who therefore will not be able to give informed consent), unless there is evidence of earlier expressions of the will to participate after information about the study was given to the patient (eg legal document)
6) Current or recent psychiatric disorder
7) Catabolic state
8) Allergy to the materials of the implant

∗ Because electrodes are already in place, imaging, electrode placement surgery and strip selection procedures are not relevant for new participants with existing implant.

4.4 Sample size calculation

Preliminary research leading up to this protocol indicates a high chance of succeeding in decoding brain activity for a switch, encouraging conception of a clinical trial. However, various factors still need to be investigated which can only be conducted with an implanted system. The parameters for evaluation of effectiveness of the BCI intervention are not straightforward (many influence each other), so we need to conduct a pilot study to investigate these factors, optimize as many as possible and then determine the appropriate indices of evaluation for a larger clinical study.
Given several defined factors that may limit performance of the system (most importantly electrode position, consistency of signal quality over time, false positive rate) we estimate success rate conservatively at 50%. Success is defined as achieving unsupervised use of the BCI system (second level of performance, see Section 2 and Section 8.1.1). Failure, on the other hand, is defined as inability to achieve the first level of BCI performance: supervised use (see Section 8.1.1 for details). One could argue that 2 participants is enough but there are too many variables that need to be taken into account that affect the outcome. Since this is a pilot study, with an adaptive trial design, chance of success can be expected to increase as we learn from participants. Moreover, for an indication of generalizability of our BCI solution, we need to include a larger numbers of participants (typically a statistical estimate can be obtained at 8 cases and up). Since this is a pilot study we have to balance the arguments of minimizing medical risks and maximizing reliability of the results. With this in mind we intend to include 5 participants. Proof of principle of our intracranial BCI solution is achieved when more than 50 % of participants is capable of unsupervised use of the system (primary objective, and see Section 8.1.1). To allow for initial failures due to unanticipated problems with the system (and suboptimal parameter settings), we will include 3 participants for certain (provided no major problems cause study termination), at which

point the results are evaluated. If all three participants fail to reach the first level of performance, being supervised use (Section 8.1.1), and convincing solutions for future participants cannot be conceived, we will reconsider continuation of the study. If one or more does achieve the first level of performance or if a convincing explanation can be given for the triple failure, we will continue inclusion of the last two participants. If all three reach the primary objective, being unsupervised use (Level 2), then we will either complete the study as planned, or we may consider initiating a larger clinical trial. We will implant patients with intervals of several months to apply obtained insights as fast as possible.

5. TREATMENT OF SUBJECTS

5.1 Investigational product/treatment

5.1.1 Device Description

Executive summary

The patient is provided with a fully implantable brain computer interface. Signals are read from subdural electrode strips (subdural leads) by an implantable device (Activa PC+S). The signals are processed in this device and transmitted subcutaneously to a handheld streaming unit. This unit sends the data to a computer (Brain Interpreter), which translates the signals into a physical switch to control assistive technology. The name and Model Number of the leads used subdurally in this study changed in 2018 from Resume II Model 3587A to Subdural Leads Model 0913025, because the Resume II leads Model 3587A have been phased out. The leads themselves are exactly the same. The term lead is used here as a pars pro toto indicating the electrode strip including its wire.

The device is a new version of the marketed deep-brain stimulator (Activa PC) for movement disorders (e.g. Parkinson's disease). A sensing part (amplifier, filters and Analog-Digital Converter) is added for sensing and recording signals for research into biomarkers and the effect of stimulation upon them. The Activa PC + S will come with CE mark for this intended use. In the current study the stimulator is disabled. The use in the UNP to use the signal for BCI control is off label. Extensive details are in IMDD Section 1.8.

Full description of procedures

The complete main configuration of the UNP system, which will be placed at the patient's home, (Figure 2) consists of the following parts:

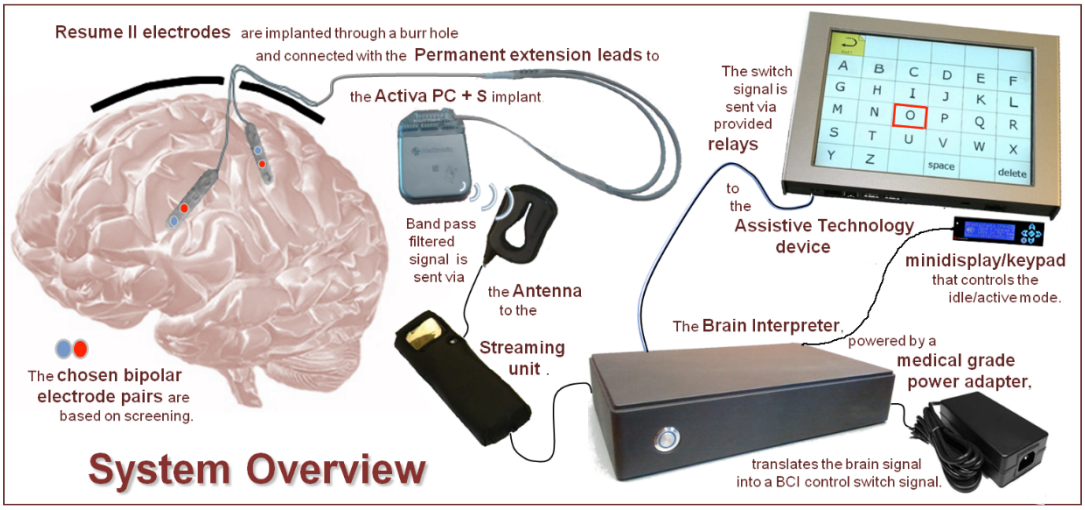

Figure 2. In the home configuration brain signals are sent from electrodes through the permanent extension leads to the Activa PC + S, which transmits the amplified and filtered

signal to the antenna connected to the streaming unit. The Brain Interpreter receives the signal, classifies it and translates it to a switch that is used to control an assistive technology device.

1. Four electrode strips with 4 electrodes each (subdural leads, model 3587A or model 0913025, Medtronic), 1 cm electrode spacing, exposed surface 12 mm^2. One strip will be placed on the dorsolateral prefrontal cortex, and three on motor areas.

2. The subdural leads are connected, via permanent extension leads, to the Activa PC+S device.

3. The Activa PC+S device (Figure 3) houses an amplifier, an analog programmable band pass filter, a DA converter and a transceiver. It will be implanted under the skin at the chest of the patient (Figure 4).

Figure 3. Dimensions of the Activa PC+S

Figure 4. Location of the Activa PC+S under the skin at the chest

4. The external receiving antenna, which communicates with the Activa PC+S device wirelessly. The antenna head will be placed in a pocket of a t-shirt that the patient will wear. Alternatively, hypo-allergenic tape, a harness or another method will be used to keep the

antenna in position, depending on what is practical and convenient for the patient and his/her caretaker.

5a. The Streaming Unit, which receives the neural signals from the Activa PC+S and sends the data in a protocol readable by the Brain Interpreter.

5b. Brain Interpreter, which receives the data from the Streaming Unit, classifies the data into two states and operates relays to simulate a physical switch as used in Assistive Technology.

6. Assistive Technology, (the 'Touchy' manufactured by KMD), which can be operated through a switch, by using a two-step (row, column) selection of fields in a matrix constituting letters or other symbols. The Touchy connects via a connection box.

7. Minidisplay/Keypad, which can be used to control idle and active mode. Moreover, this device can be used for training purposes (see Section 8).

Device settings are implemented by the research team using the following two configurations:

8a. A Sense Programmer Transmission Module (SPTM), which, together with the sensing programmer (8b) will be used to set parameters in the Activa PC+S. The SPTM has the same hardware as the streaming unit, but different firmware. The SPTM is not in the above picture, as it is only used for adjustments of parameters by the research team.

8b. Sensing programmer, which can send control data via the SPTM to set parameters in the Activa PC+S. The sensing programmer is not in the above picture, as it is used only for settings by the research team.

9. A research laptop will be used to set parameters in the Brain Interpreter. The laptop connects via a dedicated network cable to the Brain Interpreter. The research laptop is not in the above picture, as it is used only for settings by the research team.

10. A clinician programmer is used for system checks (electrode impedance, battery level). The programmer is not in the above picture, as it is used only during research visits.

The electrodes and the extensions will be implanted during the first surgery (Section 8.3.66). The extensions will be tunneled and leave the body via the abdomen. For selection of the optimal electrodes, all electrodes will be connected to the clinical Micromed intracranial EEG system, which allows recording of all electrodes (and therefore assessment) simultaneously (Section 6). During the second surgery approximately 3 days later, the Activa PC+S device will be implanted under the skin of the chest, and two of the four leads will be connected. The other leads will be disconnected from the extension and the ends will be capped (Section

8.3.6). After the second surgery, the patient will be trained on using the Switch BCI (Section 8.3.9 and 15.4). The primary control signal (bipolar signal, power in the predefined frequency range) will be transmitted continuously at 2.5-5 Hz to the Streaming Unit. This signal is sent to the Brain Interpreter, which classifies that data into two states and operates relays to simulate a physical switch which is then used to control the Assistive Technology device.

People involved

Neurosurgery team
ECoG team
Principal Investigator
Research Team

Responsibilities

The neurosurgery team is responsible for all medical acts related to the implantation of the subdural electrodes, tunneling of the wires, connection of the wires to the Activa PC+S and the implantation of the Activa PC+S under the skin of the patient.

The ECoG team confirms good signal quality during surgery. The research team is responsible for all tests and signal analysis in the course of the electrode selection and BCI training procedures. The principal investigator will have a decisive role in the electrode selection.

5.2 Use of co-intervention (if applicable)

Not applicable

5.3 Escape medication (if applicable)

Not applicable

6. INVESTIGATIONAL PRODUCT

6.1 Name and description of investigational product(s)

The Utrecht Neural Prosthesis (UNP) is a system to control assistive technology directly from signals generated in the brain. The device is intended to be used by patients with severe incapability to control any muscle to give them a means of communication and control of their environment. Towards the end of the study the patient uses the system independently at home.

The UNP consists of several parts assembled into one system by the UNP research team at UMC Utrecht. Many parts are manufactured by Medtronic. Although these Medtronic parts are CE certified (except for the Streaming Unit), their use in this system is beyond the intended use described in the CE certificate of the different parts. This is described in detail in the IMDD Section 1.

In the course of the study procedure there are 6 configurations of the UNP system. These are described in detail in D2 (IMDD Section 1.1). The configuration for home use by the patient (configuration 1) is the main goal and operates as follows:

Configuration 1: The signals are read from subdural electrode strips (subdural leads) via permanent extension leads by an implantable device (Activa PC + S). The signals are processed in this device and wirelessly transmitted transcutaneously via an antenna to a Streaming Unit. This Streaming Unit sends the data to a computer (Brain Interpreter), which translates the signals into one or two physical switches, which is a standard way to control an assistive technology device. Attached to the Brain Interpreter is a mini display/keypad to display status information and feedback to the user and to access a small menu by the caretaker. With the assistive technology device the patient will be able to communicate and have some environmental control.

To set optimal parameters for feature selection, classification and translation and for research purposes five more configurations of the UNP system are used during the study (described in IMDD Section 1.1):

Configuration 2: The implant procedure consists of 2 surgeries: one to implant electrodes, permanent extensions and temporary percutaneous extensions, and a second surgery to implant the Activa PC+S and connect the electrodes subcutaneously. At the first surgery the electrodes and permanent extensions are implanted (see Section 8.3.6) and the leads are temporarily connected percutaneously to the clinical ECoG acquisition system for electrode selection. Configuration 2 thus consists of the electrodes, permanent extensions, temporary percutaneous extensions, trialing cable and touchproof adapter and the clinical ECoG system.

Configuration 3: At the second surgery, after the electrodes are selected (see Section 8.3.7), the Activa PC + S is implanted (see Section 8.3.6) and the signals are led into a research laptop for training. This setup will be also be used at home during visits of the research team. Configuration 3 thus exists of the subdural leads , permanent extension leads, Activa PC + S, antenna, streaming unit, IrDA to RS232 converter and laptop.

Configuration 4: To set device parameters special programming equipment needs to be connected temporarily to the UNP system, thereby posing another configuration. The Activa PC + S is configured by using a dedicated Sense Programmer computer. Configuration 4 thus exists of the subdural leads, permanent extension leads, Activa PC + S, antenna, SPTM, IrDA to USB converter and Sense Programmer.

Configuration 5: To set the remaining parameters of the UNP system, the Brain Interpreter is connected temporarily with a laptop via a remote desktop connection. Configuration 5 thus is the same as configuration 1 where the Brain Interpreter is directly connected to the laptop using a USB Ethernet converter and a cross-linked network cable. The assistive technology device is not connected in this setup.

Configuration 6: System checks with the Activa PC + S (impedance measurements and battery level) are done with a clinician programmer during research visits. Also a warning message is set in the Activa PC + S with this programmer prior to implantation to prevent accidental activation of stimulation by a neurologist unfamiliar with the study. This programmer has a built-in antenna to communicate directly with the Activa PC + S.

6.2 Summary of findings from non-clinical studies

The Activa PC+S has been validated in two animal models. Using a longterm implantation in an ovine, it was demonstrated that it is capable of measuring and detecting relevant neuronal activity (in this case seizure activity) (Stanslaski et al., 2011). In addition, the ability of the Activa PC+S to process and classify brain states was demonstrated using real time BCI experiments by a non-human primate with implanted ECoG electrodes (Rouse et al., 2011). The ability of the Streaming Unit to stream signals from the Activa PC+S has been validated in a sheep model (see D2, IMDD). Chronic use of platinum electrodes embedded in silicone shows negligible tissue changes after 25 weeks subdural implant as assessed with histology in an animal study (Henle et al., 2011).

6.3 Summary of findings from clinical studies

Clinical evidence has been gathered for all aspects of the device design:

- ECoG based BCI control with working memory
- ECoG based BCI control with motor imagery
- fMRI guided localization of brain functions for BCI control and electrode placement
- Separation of different movements
- Control of a switch

- Use of Activa PC + S for BCI control : Safety and Performance
- Classification of intended and unintended commands

Each of these is described in more detail below, and (except separation of different movements) in Sections 15.1 and Annex VIII of the IMDD (D2).

ECoG based BCI control with working memory

We investigated whether voluntary BCI control can be achieved by mental calculation using electrodes subdurally placed over the frontal cortex. We used performance (percentage targets hit) in a two target cursor control task as measurement. In six out of seven patients we reached performance over 80%, which is the lower level of proficiency (see Section 8.1). Data of three patients are published (VanSteensel et al., 2010).

ECoG based BCI control with motor imagery

We investigated whether we could replicate results with voluntary BCI control by motor imagery using electrodes subdurally placed over the premotor cortex. We used performance (percentage targets hit) in a two target cursor control task as measurement. In one subject we reached 91.4% performance. Data is published (Hermes et al., 2011b).

fMRI guided localization and electrode placement

Localization was defined from data acquired during an fMRI localizer task with a patient with intractable epilepsy. Coordinates of the strongest activating voxels within a predefined Region of Interest were used to select pairs of electrodes who were implanted subdurally in the patient. This was tested retrospectively with data of patients performing BCI control with a unipolar electrode. It was tested prospectively in two patients who performed BCI control with a bipolar electrode. In both of the latter cases, excellent electrode pairs were found, with high BCI performance. For a detailed description see Section 15.5.

Control of a switch

We investigated whether ECoG signals can be used to control a switch in two epilepsy patients. The ‘clicks’ generated are the input for an Assistive Technology device, that uses these clicks to select letters in a matrix. We demonstrated that both subjects are able to type on an AT device (Touchy) using a brain- controlled switch.

Separation of different movements

To allow for the generation of multiple clicks, different movements need to be distinguished from one another from the sensorimotor cortex signal. An earlier study has shown that it is possible to distinguish the movement of individual fingers of the same hand using high-frequency band power changes (Miller et al., 2012) measured with 1-cm resolution electrode grids. In addition, movements of the ipsilateral and contralateral hand induce different activation patterns in the sensorimotor cortex, which can be distinguished from one another based on the ECoG signal (Wisneski et al., 2008; Scherer et al., 2009). Recent data from our own lab has confirmed the different representation of ipsilateral and contralateral movements and of movements of individual fingers (Schellekens et al, 2018).

Use of Activa PC + S for BCI control: Safety and Performance

We conducted safety tests, which were all passed. Performance of the Activa PC + S was verified in several stages. Performance of the Activa PC + S was compared with performance using the clinical Micromed intracranial EEG system. Performance was measured as percentage target hits in a two target cursor control task. We found that performance of the Activa PC + S is similar to the performance using the clinical Micromed intracranial EEG system.

Classification of intended and unintended commands

We tested simple and more advanced classification schemes to distinguish two states (‘yes’/’no’) in ECoG signal of epilepsy patients. Classification with thresholds is used for control of an assistive technology device in realtime. More advanced classification is analyzed offline on data recorded during a task and in outside task performance. Both schemes result in high performance, but the false positive rate is reduced with more advanced classification. The latter result is published in Torres Valderrama et al., 2012.

6.4 Summary of known and potential risks and benefits

The risk analysis (D2, IMDD Section 7) identifies several risks to the patient. Some parts of the UNP are not CE marked or not CE marked for the intended use in the UNP.
These risks are all mitigated. The most notable risks and their mitigation are:

- The system does not work satisfactory to the patient. This is mitigated by the positive results during extensive clinical validation (D2, IMDD Annex VIII). The adverse effect is low; it causes disappointment to the patient.

- The system may cause inadvertent effects in the patient’s environment (eg damage caused by controlling a wheelchair). This is mitigated by restricting the use of the AT device in the instructions to the patient and caretakers (D2, IMDD Annex II) and patient information (E1, Information letter).

- Incorrect parameter settings or procedures. This is mitigated by 1) restricting access to parameters by the research team in the instructions to the patient and caretakers (D2, IMDD Annex II) and 2) the research team will not change experts during the entire study.

- The long-term use of the electrodes may cause adverse effects. This risk is mitigated by the positive results of an acute toxicology assessment and an ongoing chronic toxicology assessment, combined with literature showing no adverse events in humans and negligible tissue changes as assessed with histology in an animal study (D2, IMDD Section 1.8).

- Unwanted enabling of stimulation of the Activa PC + S. This is mitigated by 1) disabling changing of the stimulation settings in the Sense Programmer. The SPTM and Streaming

Unit are capable to choose from stimulation patterns if preprogrammed in the Activa PC + S Therefore, 2) no stimulation patterns are programmed (D2, IMDD Section 1.8). Additionally 3) a warning for clinicians is set in the Activa PC + S and the patient dossier not to turn on stimulation.

- Allergic reaction to the used materials. This is mitigated by excluding patients with known allergies to the used materials.

If the study succeeds patients will obtain a new means of communicating with others and with their environment that cannot be obtained in any other way. It will enable patients to engage in interaction at any time, and without the help from others. This is expected to increase their quality of life.

6.5 Description and justification of route of administration and dosage

N.A. (no medicinal product)

6.6 Dosages, dosage modifications and method of administration

N.A. (no medicinal product)

6.7 Preparation and labelling of Investigational Medicinal Product

N.A. (no medicinal product)

6.8 Drug accountability

N.A. (no medicinal product)

7. NON-INVESTIGATIONAL PRODUCT

N.A. (no medicinal product)

7.1 Name and description of non-investigational product(s)

7.2 Summary of findings from non-clinical studies

7.3 Summary of findings from clinical studies

7.4 Summary of known and potential risks and benefits

7.5 Description and justification of route of administration and dosage

7.6 Dosages, dosage modifications and method of administration

7.7 Preparation and labelling of Non Investigational Medicinal Product

7.8 Drug accountability

8. METHODS

8.1 Study parameters/endpoints

8.1.1 Main study parameter/endpoint

Primary endpoint is proficiency of use of the BCI system. For this we recognize three levels of proficiency: First, the level of proficiency described as the primary objective, being *unsupervised BCI performance* (with the caregiver enabling / disabling AT device), with the criterion that the system correctly detects a switch brain signal within 10 sec in a real life, cognitively engaging context, such as operating a spelling device. A formal test has been designed, in which the patient has to copy a 30 character sentence within 30 minutes, with a margin of 20% faulty characters (see Section 8.3.9, Level 2 proficiency). For this test, scanning software is employed. Second, we define a lower level of proficiency, which represents a level equivalent to that of the communication channel that the patient had before participation, being *supervised BCI performance*, where the patient is able to generate switch commands with at least 80 % correct, with the help of a BCI researcher and/or caregiver (using a formal test, see Section 8, Level 1 proficiency). A third level of control is defined as *independent BCI performance*, where the patient is capable of enabling/disabling AT device control by himself. This requires the highest level of control achievable.

Thus, the three levels, in order of proficiency are:
1) Supervised use, dependent on continuous assistance for communication
2) Unsupervised use, ability to communicate without assistance for limited periods
3) Independent use, ability to communicate without assistance at any time of day or night.
Note that level 2 is the primary objective of the study, and that only levels 1 and 2 will be tested using formal tests. Success of the study is defined as: At least 50% of participants (3/5) reach level 2 proficiency and can thus communicate effectively as assessed with a formal test.

8.1.2 Secondary study parameters/endpoints (if applicable)

Secondary study parameters are patient satisfaction (subjective ratings, hours use of BCI system per week, quality of life), and definition of a set of metrics for evaluation of efficacy of the BCI system for a larger clinical trial.
In the case of unreliable communication at the time of inclusion, secondary study parameters can only be investigated if the patient can use the UNP system to communicate reliably.

8.1.3 Other study parameters (if applicable)

Not applicable

8.2 Randomisation, blinding and treatment allocation

Not applicable

8.3 Study procedures

8.3.1 Presurgical Testing – Psychology and Neuropsychology

Executive summary

After the informed consent procedure, the patient undergoes a number of psychological and neuropsychological tests, in order to confirm that the patient is not currently suffering from a major depression, and to estimate the level of cognitive functioning of the patient. Based on the outcome of the depressive symptoms test and the cognitive functioning test it will be decided whether the patient will continue in the following steps of the study. Further the quality of life of the patient is assessed. This test will be repeated multiple times after implantation to quantify the changes over time. Finally, the opinion of the patient about the importance about certain aspects of a BCI will be determined. These two parameters will be used to address Secondary Objectives 1 and 2 (see Section 2). All of the tests have been adapted for use by locked-in people.

In the case of unreliable communication at the time of inclusion, psychological and neuropsychological tests can not be conducted. In this case, a result of (f)MRI analysis where there is a clear correlation with the task design will be taken as evidence that the patient is capable of understanding and following instructions, and consequently as indication of sufficient cognitive functioning for participation in the study. Presence or absence of depressive symptoms is evaluated in consultation with the primary caregiver and legal guardian.

Full description of procedures

After the patient has given informed consent to participate in this study the patient will perform a set of psychological and neuropsychological tests to determine depressive symptoms, to test the cognitive capacities and the quality of life of the patient, and to determine his/her opinion about the importance of certain aspects of the BCI. The testing takes place at the patient's home. For patients living abroad, the testing will take place at the UMCU. A clinical neuropsychologist of the department Neurology and Neurosurgery of the UMC Utrecht conducts and interprets the tests. The patient will use his means of communication to respond to the tests. All test questions are either 'yes'/'no' or multiple choice questions and therefore allow assessing patients with limited means of expressive communication.

In the case of unreliable communication at the time of inclusion, the legal representative will give informed consent, the psychological and neuropsychological tests are not conducted, and presence or absence of depressive symptoms is evaluated in consultation with the primary caregiver and legal guardian.

Depressive symptoms

The patient is tested on depressive symptoms using the ADI-12 (Section F1.5) depression inventory (Hammer et al 2008), which comprises 12 statements. The patient has to indicate how much he agrees with each statement on a 4-point scale. A score of 30 or higher is

associated with a current episode of major depression. A patient is excluded from the study if the ADI-12 level is 30 or above. The test lasts approximately 20 minutes.
In the case of unreliable communication at the time of inclusion, presence or absence of depressive symptoms is evaluated in consultation with the primary caregiver and legal guardian.

Cognitive functioning

The cognitive functioning of the patient will be assessed using three tests:

1. Raven's advanced progressive matrices, set 1 (Raven 1948; Raven et al., 2003). This test consists of a set of 12 non-verbal multiple choice measures of general intelligence. In each test item, the subject is asked to identify the missing element that completes a pattern. The score that patients have will depend on their age and education level. Patients having a score that corresponds to an IQ of <80 will be excluded from further study. The test has no time limitations; it will take about half an hour (+- 15 min) depending on the patient.

2. The Peabody test (Peabody Picture Vocabulary Test) will be used to measure speech comprehension. For this test, the patient is instructed to match a verbal stimulus to one of four images. Chosen images are marked by the assessor after confirmation. Verbal stimuli are words that are read to the patient. The average score of a twelve year old child with normal intelligence is 130. This is the minimum performance level the patient has to score to be included in the further study. The test has no time limitations. Depending on the performance of the patient this task lasts between 20 and 60 minutes.

3. A mental calculation task will be used to test mathematical skill (Vansteensel et al., 2010; Ramsey et al., 2006). The patient is presented with 20 equations of two levels of difficulty with a given answer (e.g. 17 + 5 = 23). The patient has to compute the result of the equation and has to decide whether the given answer is right or wrong. The patient has to have 80% of the easy sums correct. The test has no time limitations; it will take about 25 minutes.

4. Visual Association Test. This test will be used to estimate the learning capacities of the patient. The patient will see a picture of two combined objects. Next, one of the two objects will be shown, and the patient will be asked which object is missing. For every item, 3 possible choices will be given. This test consists of 6 trials and will take about 10 minutes to complete.

In the case of unreliable communication at the time of inclusion, tests of cognitive functioning will not be conducted and results of fMRI analysis will be informative for the neuropsychologist about the patient’s cognitive ability to understand and follow instructions.

Quality of life

As part of addressing Secondary Objective 1 (Section 2), we assess the quality of life of the patient throughout the study. This first test serves as baseline measure. The so called Anamnestic Comparative Self-Assessment (ACSA) will be used for this assessment (Bruno et al., 2011), whose biographical +5 and -5 scale anchors the patient's memories of the best period in their life and their worst period ever. The test will take about 10 minutes to complete (Section F1.6). The test will be repeated on several occasions after the implantation of the electrodes, in order to monitor whether quality of life changes over time (See Sections 15.4 and 8.3.10).
In the case of unreliable communication at the time of inclusion, quality of life test can only be conducted if the patient can use the UNP system to communicate reliably.

Importance of Device Aspects

As part of addressing Secondary Objectives 1 and 2 (Section 2), the opinion of the patient about the importance of a range of aspects of the device will be determined using a dedicated questionnaire. The patient will rate each item on a four point scale that ranges from 'not at all important' to 'very important' (See Section F1.8A). This test will be repeated at the end of the study to monitor any changes. At that moment, the satisfaction of the patient about each of these issues will be measured too (see Section F1.8B).
In the case of unreliable communication at the time of inclusion, device questionnaires can only be conducted if the patient can use the UNP system to communicate reliably.

People involved

Neuropsychologist
Member of the Research Team

Responsibilities

The neuropsychologist is responsible for taking the presurgical psychological and neuropsychological tests and interpreting them. The member of the research team will be present for observation and help. The member of the research team will perform the postsurgical quality-of-life tests.

8.3.2 Presurgical testing – Medical

Executive Summary Anesthesiologist

This section describes the measures that are taken to make sure that the patient will have no negative consequences from the surgical procedures. The checkup by the anesthesiologist shortly before surgery will be according to regular medical practice. The procedure has one additional visit by an anesthesiologist to the patient's home before admission, to minimize the chance that the patient will be excluded from the procedure after he has already been admitted to the hospital.

Full description of procedures

About 1 week before admission, the patient will be visited by a member of the anesthesiology team, who will verify that the physical condition of the patient is sufficiently good for the surgical procedures. For patients living abroad, the testing will take place at the UMCU. If the anesthesiologist decides that the physical health is insufficient, the patient will be excluded from the study.

On day 1 of admission to the hospital, patients will be seen by an anesthesiologist, according to standard medical practice, to inform the patient about the surgical procedure, and to once more verify that the patients physical health is sufficient for the implantation surgery and to make sure that the patient is not at risk of irreversible respiratory problems as a result of the surgery. Patients who are judged to be insufficiently healthy for the implantation procedure will be excluded from the remainder of the procedure and will return home. The chance that this actually happens will be minimal due to strict inclusion and exclusion criteria, and the extra check-up that patients will have before their admission to the hospital.

People involved
Members of the anesthesiology team

Responsibilities
The anesthesiologist is responsible for judging whether the health of the patient is sufficient for the surgical procedures that are scheduled.

Executive Summary Neurologist
This section describes the measures that are taken to objectify neurological parameters before and after surgery. The examinations by the neurologist shortly before surgery and after surgery will be according to regular medical practice.

Full description of procedures
During pre-operative work-up, eligible patients will undergo physical neurological examination by a neurologist (45-60 mins). Neurological examination will consist of:

1. Complete evaluation of neurological systems for as far as the communication problems and paralysis allow. This includes consciousness, cognitive functions, cranial nerve function, and investigation of the extremities (muscle strength and tone, sensory functions, coordination and reflexes).
2. Systematic and thorough mapping of (residual) motor function (MRC grades) and sensory function (preservation of pain and touch).

Post-operatively, early and (if needed) late post-operative neurological examination will be performed, with focus on changes compared to the pre-operative neurological status (30 mins).
In the case of unreliable communication at the time of inclusion, tests that require communication will be replaced by consultation with the primary caregiver and legal guardian.

People involved
Neurologist

Responsibilities
The neurologist is responsible for a neurological report.

8.3.3 Presurgical Testing – fMRI ∗

Executive summary
The results of fMRI scans are used to determine where electrodes will be positioned on the brain, for each participant separately. Regions of Interest have been defined based on prior fMRI research in epilepsy patients who participate in the BCI research at the UMC Utrecht, and healthy volunteers. Activity within these Regions of Interest is evaluated for reliability and the locations are used by the surgeon during electrode placement. This section describes the complete protocol of the fMRI part in the UNP study. This includes step-by-step descriptions of the fMRI procedure from several weeks before the admission of the patient to the hospital until the final analysis for the fMRI data for prelocalizing the brain regions for surgical implantation.

Full description of procedures
When patients are found to be physically and mentally sufficiently healthy, patients will perform an fMRI scan, in order to prelocalize brain regions involved in motor imagery/attempt as well as mental calculation. The procedure for this scan involves the following steps:

- An fMRI screening form will be filled out by telephone during the first contact with the patient/caregiver, in order to make sure that the patient is MRI compatible and can actually be included in the study (Section F1.2).
- About 2 weeks before admission, patients will receive instructions for the tasks that need to be performed in the scanner (Section E1.2)

∗ Because electrodes are already in place, imaging, electrode placement surgery and strip selection procedures are not relevant for new participants with existing implant.

- About 1 week before fMRI scan, patients will be visited by members of the research team, in order to practice the tasks. Attempts will be made to verify that the patient understands the tasks and is able to perform them correctly.
- The fMRI scan itself will be performed on Day 1 of admission. Patients will first repeat the task practice, and then continue to perform the actual fMRI scan. The MRI data acquisition will take place in the clinical 3T MRI scanner located at the Radiology Department of the UMC Utrecht. Scans will be performed by a trained technician and members of the research team. Special care is taken to ensure that patients have no metal objects present in the body. Of particular concern are metal fragments in brain tissue or eyes, surgical clips and non-removable electronic devices, such as pacemakers. If in doubt, we will schedule X-ray photos of the head on the same day before MRI to verify MRI compatibility. Fiduciary markers will be placed by a member

of the neurosurgical team on the patient's head to allow for surgical mapping, according to standard clinical practice (Section 15.3). Patients who need glasses will receive nonmagnetic glasses, because frames tend to disturb the magnetic field. In the scanner support of the head will be evenly distributed, to avoid local pressure. Patients will receive earplugs to dampen the scanner-noise. Since the patients will likely be dependent on artificial ventilation, the Department of Anesthesiology will be responsible for the transport between the Intensive Care Unit or Intensive Epilepsy Monitoring Unit (depending on the requirements of artificial ventilation) of the UMC Utrecht and the MRI scanner and the relevant respiratory equipment. A Standard Operating Procedure (Section 15.1) has been written for this. During MRI scanning, a member of the anesthesiology team will be present in the scanner room to monitor wellbeing of the patient. In case of a patient who does not need artificial ventilation, heart rate and respiration will be monitored via standardized scanner-equipment by the technician who controls the scanner. In addition, a member of the research team will be present to watch the patient and to communicate with him/her through the available communication channel, for example via an eye tracker. An emergency button will be available in order to stop scanning when necessary. This button will be controlled by the researcher or the anesthesiologist. In case a participant cannot communicate reliably at the time of inclusion, communication via an eye tracker during the scan will likely not be possible. In these cases, the vital signs will be informative about the wellbeing of the patient. In consultation with the caretaker, one or more interruptions of the scan session may be scheduled for extra checkups and care if needed. During the whole procedure, it is possible to speak to the patient and with the people in the scanner room via the MRI intercom system. During scanning, patients are presented with instructions on a video screen. The patient can see the screen through a mirror fixed to the head coil.

- The scan protocol is as follows:
    - Anatomy + neuronavigation marker scan (5 min)
    - Reference scan (1 min)
    - 2 scans to map the motor cortex (9 min each), 1 focusing on ipsi- and contralateral (attempted) movement and 1 focusing on individual finger (attempted) movements
    - 2 scans to map regions involved in mental calculation (15 min and 9 min)
    - angiographic scan (10 min)
    - Total duration of the actual scanning: ~58 minutes
- For analysis of the fMRI data, functional scans will be realigned, co-registered with the anatomical scan using a reference scan (FA27 scan) and fitted to a General-Linear-Model (GLM) using SPM8 software (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). No spatial smoothing will be applied since data are analyzed on an individual patient basis. The t-maps are used to determine the exact positioning of the electrodes. For validation see Section 15.5. After the first fMRI scan, it will be determined whether the fMRI activation pattern of one or both of the approaches (motor imagery/attempt or mental calculation) are

usable, and the two regions that are the most promising for successful BCI control will be selected. If the results of the fMRI analysis do not allow a clear localization of the target areas, the fMRI scan will repeated on the next day. If the results of the second scan are also ambiguous, the patient will be excluded from the study. Additionally, the level of cerebral atrophy will be judged. In case of excessive generalized atrophy, the patient will be excluded from further study. If the fMRI data are satisfactory, the following procedure is applied. T-maps are co-registered to the anatomy allowing for projection of t-value onto the cortical surface. A specialized program is used (Mricron, http://www.mccauslandcenter.sc.edu/mricro/mricron/) to remove skin and skull (routine based on FSL software from Oxford, UK). Then, the T-map is merged with the anatomical brain data. A 3D rendering is then made with fMRI activity in color (red for voxels exceeding a set threshold), projected onto the cortical surface (grey). Given our extensive experience with individual t-maps for clinical fMRI scans for neurosurgery, we will not apply a fixed cutoff for significance, but we will identify the peak t-values within predefined Regions of Interest. The brightness of the red color indicates the height of the t-value. The predefined Regions of Interest are based on preparatory research (Vansteensel et al., 2010; Ramsey et al., 2006; Hermes et al., 2011b), and include the border region between left hemisphere F1 and F2 (Brodmann areas 9 and 46) for working memory, and premotor/motor region (Brodmann area 4 and 6) for motor imagery/attempt (see Section 15.5). Based on the patterns of activity around the peak values, the exact location and orientation of the 4 electrode strips is determined. One strip will be aimed at the dorsolateral prefrontal cortex, and three strips are placed over the sensorimotor cortex, aimed at covering areas of ipsilateral and contralateral hand and finger (attempted) movement. Exact position is drawn on the surface within the MRIcron program and coordinates of each electrode are recorded in native space. Next, the coordinates are converted to a single mask file which will contain 16 white dots in the same space as the anatomy. The anatomy and the electrode mask are then merged. Finally, the merged file is read into the Stealth Neuronavigator in the Operating Theatre. At the start of surgery the head is then co-registered with the anatomy scan using the fiducials or bone screws (for bone screws see below). Based on the exact locations of electrodes on the MRI scans, a set of 4-8 burr holes are made and the four electrode strips are implanted under the dura (see Section 8.3.6)

People involved

Member(s) of the research team
Member(s) of the anesthesiology team
Member(s) of the radiology team/ trained technician
Member of the surgical team
Principal Investigator

Responsibilities

The surgical team will be responsible for correct placement of the skin fiducials. The radiology team is responsible for controlling the scanner and the safe placement of the subject on the scanner bed. The anesthesiology team is responsible for safeguarding the respiratory function of the patient during transport through the hospital and during the fMRI scan itself. The research team is responsible for communication with the patient (or legal guardian), task presentation to the patient and data analysis. Data interpretation and decisions about the implant locations will be made by the Principal Investigator.

8.3.4 Presurgical testing – EEG

The EEG measurement session may take place several weeks or days before hospital admission, or at a suitable time after implantation of the electrodes and the device. The electrodes of a 64-channel EEG headcap will be put in contact with the head (this takes about 30 min). Data is acquired with a dedicated EEG registration system. After fitting the EEG cap, the measurements start and instructions and stimuli are displayed on a monitor visible to the participant. Participants will perform a baseline (rest) task and tasks to activate the motor cortex and the regions involved in mental calculation (see section 8.3.7 for a description of the localizer tasks).

8.3.5 Presurgical testing – Neuronavigation scan ∗

In case a patient had the fMRI scan several weeks before electrode implantation, a presurgical neuronavigation MRI (30 min) or CT scan (20 min) will be made on Day of admission. The decision for an MRI or CT scan will be done by the neurosurgeon, taking into account the electrode implantation plan. During preparation for the neuronavigation scan, 4-8 fiduciary markers or bone screws will be placed by a member of the neurosurgical team on the patient's head to allow for surgical mapping, according to standard clinical practice. MRI and CT scans will be performed by a trained technician and members of the research team. In the scanner, support of the head will be evenly distributed, to avoid local pressure. During the whole procedure, it is possible to speak to the patient via the MRI/CT intercom system. In the case of a neuronavigation MRI scan, precautions and safety measures will be the same as described above for the fMRI scan.

∗ Because electrodes are already in place, imaging, electrode placement surgery and strip selection procedures are not relevant for new participants with existing implant.

8.3.6 Surgery

Executive Summary

This section describes in detail the surgical procedures of two surgeries. In the first surgery the electrodes will be placed on the two target regions. In the second surgery the device will be implanted and the electrodes will be connected (Section 5). Standard operating procedures have been designed for both surgeries (see Section 15.6).

Full description of procedures

Procedure 1 ∗

The patient is subject to normal peri-operative procedures used at the department of neurosurgery at the University Medical Center Utrecht. Prior to surgery the patient will undergo a preoperative anaesthesiological screening. After completing one checklist (SURPASS, see Section 15.7) by the resident, one by the nurse and one by the neurosurgeon responsible for the procedure, the patient is transferred to the holding area of the OR center. An intra-venous canula is placed and connected to a Saline drip to prevent the canula from clotting. If the patient is on a ventilator he is transferred to the recovery area of the OR center. From there the patient is transferred to the operating theatre. The patient receives general anesthesia after completing the briefing and time-out procedure (SURPASS) with the anesthesiologist, neurosurgical scrub nurses and the neurosurgeon. As with all neurosurgical procedures 2 grams of cefazolin is prophylactically administered intravenously 30 minutes before skin incision.
The position of the electrode strip is guided by the intraoperative neuronavigation system (Stealth / Medtronic) using fMRI data, as well as using the 3D cortical surface renderings of the fMRI scans. The MRI fiducials or bone screws are co-registered into the neuronavigation system. A maximum of 2.0 mm accuracy offset of the navigation system is accepted. One procedure (placement of three electrode strips, each consisting of four electrodes) is performed over the motor region and one procedure (placement of one electrode strips, each consisting of four electrodes) is performed over the working memory region of the dorsolateral prefrontal cortex. In principle, two burr holes will be used for the accurate positioning of each electrode strip, one small burr hole (site B) at the center of electrode 0 (the electrode furthest from the connecting lead), and one larger burr hole (site A) at the exit point of the electrode lead. In case the two strips are planned to be located parallel and directly next to each other, two slightly larger burr holes will be used.

∗ Because electrodes are already in place, imaging, electrode placement surgery and strip selection procedures are not relevant for new participants with existing implant.

A Mayfield system is used to fixate the skull. The skin is disinfected with chlorhexidine and covered with Ioban. A linear skin incision is made between sites A and B of each projected electrode strip. The skin and galea are separated from the skull. The sites A and B are marked on the skull using the neuronavigation system. Burr holes are made on these markings by an automated drill (Anspach system). This drilling system automatically stops before entering the dura. The dura then is superficially diathermically coagulated, and a dura incision is made.
The area under the dura is inspected with a ‘dura probe’, and checked for venous blood vessels. An electrode strip will be guided subdurally from site A to site B. Its position is checked by making sure that centre of electrode disc 0 is visible in the centre of the burr hole at site B. At site A, a small groove will be made in the skull at an angle of about 45º, which will be used to guide the electrode lead. Over the groove and the lead, a low profile scull fixation plate will be placed to fixate the lead. Both burr holes are closed watertight with Tachosil.

After placing a maximum of four strips, the subdural leads are tunneled subgaleally to the area where the connectors will be placed (preferably temporoparietal at the hemisphere of implantation). In this temporoparietal area, a linear incision is made, allowing access to the connectors. The permanent extensions (type 37087) are tunneled from this incision cranial to caudal to the thorax, opened with a linear skin incision. The extensions are marked by a wire-specific Mersilene ligature at the thorax level and connected watertight to the subdural leads. The temporary extensions (type 37081) are connected watertight to the permanent extensions in the thorax and tunneled to the abdomen, where they are externalized and fixed to the skin with Mersilene ligatures. The extensions will also be specifically marked by Mersilene ligatures.
The externalized side of the extension leads is connected to the external recording equipment with a snaplid connector. This connector is sealed watertight in the bandage that is applied after surgery. All skin incisions are closed in two layers. During the testing period, prophylactic cefazolin antibiotic treatment will be administered.

Procedure 2

The patient is subject to normal peri-operative procedures used at the department of neurosurgery at the University Medical Center Utrecht. Prior to surgery the patient will undergo a preoperative anaesthesiological screening. After completing one checklist (SURPASS, see Section 15.7) by the resident, one by the nurse and one by the neurosurgeon responsible for the procedure, the patient is transferred to the holding area of the OR center. An intra-venous canula is placed and connected to a Saline drip to prevent the canula from clotting. If the patient is on a ventilator he is transferred to the recovery area of the OR center. From there the patient is transferred to the operating theatre. The patient receives general anesthesia after completing the briefing and time-out procedure (SURPASS) with the anesthesiologist, neurosurgical scrub nurses and the neurosurgeon. As with all neurosurgical procedures 2 grams of cefazolin is prophylactically administered intravenously 30 minutes before skin incision.
The skin is disinfected with chlorhexidine and covered with Ioban. The linear skin incision at the thorax will be re-opened and the permanent extensions are disconnected from the temporary percutaneous extensions. The connectors of the temporary extensions will be cut, allowing removal of the extensions by traction at the location where they are externalized.
A subcutaneous pouch is made at the thorax subclavicular.

Two permanent extensions (type 37087) are watertight connected to the Activa PC+S device. The tips of the other primary cables are capped. The Activa PC+S is placed in the pouch and fixated. The connected extension leads are buried behind the Activa PC+S. The skin incisions are closed in two layers. The patient is prophylactically kept on cefazolin for two consecutive days.
In case of a participant with an existing implant, after opening of the subcutaneous pouch, the connected electrode leads are disconnected from the Activa PC+S and two of the implanted leads are watertight connected to a new Activa PC+S device (these may be

different leads than the ones originally connected). The explanted materials are disposed of as infectious and hazardous medical waste according to European Waste Catalogue nr. 18 01 03.

Responsibilities

The anesthesiologist is responsible for the anesthesiology related procedures. The neurosurgeon is responsible for the surgical procedure. A dedicated and trained subgroup of the research team will be responsible for the availability of the device and its accessories on the OR (see also Section 15.6).

8.3.7 Operating Theatre tests and Electrode Selection Procedure∗

Executive Summary

This section describes the procedure of signal quality evaluation during surgery, as well as the methods for electrode selection. In the period between the two surgeries a number of localizer tasks will be performed to find the best electrode strips for connection to the device in the second surgery.

Full description of procedures

During first surgery

In the operation room the quality of the recorded signal is evaluated as soon as the electrodes are in place. This is to assure the general technical integrity of the placed electrodes and their respective extensions as well as the contact between electrode and cortical tissue.

∗ Because electrodes are already in place, imaging, electrode placement surgery and strip selection procedures are not relevant for new participants with existing implant.

For this assessment the standard clinical procedure performed during grid implantation in epilepsy patients will be used. An expert from the ECoG Team will evaluate the signal quality assuring that the electrodes have good contact with the brain and that all connections (electrode and extensions cable) are in good order. For this purpose, the electrodes will be connected to the standard clinical Micromed intracranial EEG system using touch-proof connectors.

After first surgery

On the first or second day after the first implantation surgery, a CT scan will be performed in order to verify correct placement of the electrodes. Together with the presurgical anatomical MRI scan, a rendering will be made to visualize the location of the individual electrodes on the cortical surface.

After the first surgery the best electrode strips will be identified during a two day screening period before the second surgery. The two day screening period can be prolonged up to 7 days dependent on patient condition and quality of electrode selection screening results. The patient is asked to perform a maximum of eight total hours of testing each day. The duration of each test and the duration between tests are subject to patient condition. All 16 implanted electrodes (see Section 5) are connected to the clinical Micromed intracranial EEG system. The data will be acquired in the time domain (512Hz sampling rate, 22bit). The data will be recorded for 24 hours every day. Cognitive control and motor imagery/attempt localizer tasks are performed (described below). These are similar to the tasks that the patient has performed in the 3T scanner. The patient gets no feedback on his brain activity. Based on this data the best electrode strips are determined. If the results of the motor tasks indicate that different hand / finger movements show different activation patterns in the sensorimotor strips, we will connect two of the three sensorimotor strips to the device in the second surgery. If the results of the motor tasks indicate overlap between the activations of the different hand/finger movements, one motor strip will be connected, as well as the dlpfc strip. The final decision of electrode strip selection will be made by the Principal Investigator before the second surgery. The Principal Investigator may decide at this time not to proceed with the second surgery if electrode selection is not possible.

During the second surgery

After the Activa PC+S is in place and the electrodes are connected, proper functioning of the Activa P+S is ensured. The Activa PC+S will be configured and the signal quality will be tested using the Sensing Programmer and the SPTM (see Section 5.1.1). Signal quality is tested by reading the time domain data. The Principal investigator will be responsible for evaluating the correct functioning of the Activa PC+S.

Analysis of localizer task data (after first surgery)

For all channel combinations within a strip the bipolar reference is computed (this leads to six bipolar channels for each strip) for the localizer tasks. The data is epoched and the power is computed for all frequencies between 1 and 120Hz. For each bipolar channel the correlation with the task (expressed as the R^2 value) is computed. The channels that show a significant R^2 value are considered possible candidates for BCI control. Channels that show a significant change in power over a broad band of frequencies (preferably between 65Hz and 95Hz) are favored. This procedure is repeated for all repetitions of the localizer task. The two channel pairs that show a consistently high R^2 are selected for being connected to the device. Based on previous experiments with epilepsy patients an R^2 of above 0.3 will be considered sufficient. This analysis is carried out by members of the Research Team.

Localizer tasks used (after first surgery)

The signal for controlling the Assistive Technology device will be generated either by cognitive control or by motor imagery/attempt. For both functions localizer tasks similar to those performed in the FMRI scanner are performed. We describe the ECoG localizer versions of the tasks here.

Localizer task - Cognitive control

In this task the patient has to count forward (in steps of one), count backwards (in steps of seven, or less depending on the abilities of the patient) or relax. Each condition starts with an instruction ('tel vooruit', 'tel terug','rust'), for the two counting conditions a start number is given. For the count forward condition a number below 10 is shown, for the count backward condition a number above fifty is shown. Each trial last 15 seconds followed by an inter-trial interval of 2 seconds in which a fixation cross is shown. The entire task lasts about 9 minutes. The patient will get the following instruction:
"Je ziet straks 3 verschillende instructies. Bij 'rust' hoef je niets te doen. Bij 'tel vooruit' ga je vooruit tellen vanaf het getal dat in beeld verschijnt, in stappen van 1. Bij 'tel terug' ga je terug tellen vanaf het getal dat in beeld verschijnt, in stappen van 7. Het duurt ongeveer 9 minuten."

Localizer task - Mental imagery of the left and right hand

In this task the patient has to imagine/attempt a movement of the ipsilateral or contralateral hand, or relax. Each condition starts with an instruction ('links', 'rechts, 'rust'). Each trial last 15 seconds followed by an inter-trial interval of 2 seconds in which a fixation cross is shown. The entire task lasts about 9 minutes. The patient will get the following instruction: *"U ziet straks 3 verschillende instructies. Bij 'rust' hoeft u niets te doen. Bij 'links' denkt u aan de beweging van uw vingers van de linkerhand /probeert u uw vingers van de linkerhand te bewegen, op het ritme waarin het blokje knippert. Bij 'rechts' doet u hetzelfde, maar dan met de rechterhand. Het duurt ongeveer 9 minuten, waarin het inbeelden van bewegen / proberen te bewegen wordt afgewisseld met pauze."*

Localizer task – Fingers

In this task, the patient has to attempt moving individual fingers (thumb, index, little finger). They see a hand on the screen, with one of the fingers in a different color: the finger they have to try to move. The task lasts about 9 minutes. The patient will get the following instruction:
"Each finger is indicated with blue shading over the hand. Try to move the indicated finger when selected (in blue), stop when you see a white cross appear in the middle of the hand."

People involved

Research Team
Expert from the ECoG team
Principal investigator

Responsibilities

The Expert from the ECoG team is responsible for implant signal quality evaluation during the first surgery.
The Research Team is responsible for localizer task administration and analysis.
The Principal investigator is responsible for the final decision regarding electrode selection of whether to discontinue with the second surgery.

The Principal investigator is also responsible for evaluating the correct functioning of the Activa PC+S during the second surgery.

8.3.8 Home Use and Data Collection

After the patient is released from the hospital, the home use and data collection period starts. During this period, patients will be trained to control the BCI accurately, and data will be collected for research purposes. Between visits of the research team, patients are allowed to use the BCI system at any time they want for practice or real communication purposes (see Section 8.3.13). During phase 1 and 2, patients can train using the feedback given by the minidisplay/keypad. During phase 3 and 4, patients can also use the assistive technology device for practice between visits.
About six weeks after the patient was released from the hospital, one of the neurosurgeons or the nurse practitioner will visit the patient for a postsurgical medical checkup.

Raw data from the Activa PC+S is saved continuously (see Section 8.3.11) to monitor signal characteristics over time (see Objectives Section 2). A log book will be provided, and the caretakers will be asked to write down everything they consider relevant for the BCI project. Notably, this information will be anecdotal and subjective. It may contribute to the BCI optimization process, but research will not depend on it.

The research team will visit the patient on a regular basis (Section 15.4). During every visit, the VAS Mood and Motivation will be performed (in case of unreliable communication at the time of inclusion, VAS evaluations can only take place after the patient has reached adequate control with the UNP) and the functioning of the BCI system will be assessed using the information written down by the caretaker in the log, and by consultation of the caretaker and/ or patient. Also, a system checkup is performed using the clinician programmer. Subsequently, several tasks will be performed by the patient for training purposes. If necessary, system adjustments (on the level of feature selection, classification and/ or translation, see IMDD) will be made to optimize BCI performance (Section 8; Section 8.3.11; Section 8.3.12). In addition, psychological and signal data will be collected for research purposes (Section 15.4).

The number of visits, and the duration of each visit, will depend on the patient's condition and BCI performance. Initially, visits will be frequent, with a maximum of two per week. A maximum of 2 extra visits may be planned for training purposes only (no research data collection), in order to quickly familiarize the patient with the system, during the first, second or third week after release out of the hospital, depending on the postsurgical condition of the patient. After appropriate BCI control has been reached, frequency of visits will decrease (Section 15.4). Visits will be planned according to schedule, and in consultation with the patient and caretakers. If, during a scheduled visit, the required data cannot be obtained (completely) due to e.g. patient condition, time availability or motivation, the (remainder of) the data may be acquired during an extra visit scheduled shortly after the incomplete

session. The experimental time per visit, i.e. the time that the patient is actually performing tasks or tests, varies between 20 min and 198 min (3.3 h, only the last visit, see Section 15.4 for an overview). The complete duration of a visit will be longer, however, because of pauses, set-up time, instruction time etc. The maximum presence of the research team at the patient's residence will be limited to 5 h per day.

The psychological wellbeing of the patient will be monitored by 1) close contact with the patient, 2) speaking with the caretakers, 3) monitoring of the VAS scores for mood&motivation and 4) the psychological questionnaires that are carried out on a regular basis. The VAS scores and psychological questionnaires will be monitored by a clinical neuropsychologist of the UMC Utrecht, and the researchers will report their observations to her as well. If the neuropsychologist feels that the psychological wellbeing of the patient is endangered, an intake will be scheduled to the outpatient center Affective and psychotic disorders of the UMC Utrecht.
In the case of unreliable communication, some of the tests test can only be conducted if the patient can use the UNP system to communicate reliably.

8.3.9 BCI Training Procedure

Executive summary

The aim is to provide the user with one or more general purpose BCI switches, which is comparable to a switch we use with our hands. For the BCI switch to work the patient has to practice to get optimal results. Our experience with grid patients shows that the state of a patient is fundamental to the BCI performance. Based on this experience the training procedure is divided into three phases. The patient will 1) be familiarized with the system, 2) learn to use the switch in a number of training tasks and 3) learn to use the switch in combination with assistive technology. When the final phase is finished, the patient will be able to voluntarily control the assistive technology and use it for communication purposes. The procedure is further defined is this section.

Full description of procedures

General Training Procedure Overview

In the ideal case the patient will be provided with one or more switches that react instantly, are activated only when the patient wants it to, and are inactive otherwise. Using broadband high frequency (65 Hz to 95 Hz) power changes we can come close to the ideal switch as our research with epilepsy patients showed. However, this requires training for the patient and fine tuning of the system parameters related to feature selection, classification and / or translation (see IMDD). Further it is our aim to study the long term effects of using an intracranial BCI, which are unknown today. The end goal is that the patient can use the switch(es) unsupervised in combination with assistive technology to communicate by typing. For this the patient undergoes a four phase training procedure. During each phase the patient will gain more control over the device. The training will take place partly in the

hospital (depending on the length of stay of the patient) and at home (see Section 15.4). The duration of each phase depends on the patient's progress.

In the first phase the patient is familiarized with the concept of a BCI and controls for the first time a cursor on a screen using changes in brain activity. In the second phase the patient is trained to control the switch(es). The main objective is to decrease the time required to elicit a switch event and to increase the accuracy, i.e. increase the number of hits while decreasing the number of false positives. In the course of phase two, the level of proficiency is tested on a regular basis using a formal test. Once the patient succeeds in this test we conclude that he has a functional switch and has reached Level 1 Proficiency (supervised use, see Phase 2 Supervised BCI Control, below). In the third phase the patient is trained to increase the accuracy even more and to use the switch(es) to control assistive technology in a real life setting (unsupervised use, see Phase 3 Unsupervised BCI Control, below). The goal of phase 3 is to allow the patient to use the switch(es) independently of the researchers. The proficiency of the patient in doing so will be formally tested using a predefined sentence on a regular basis (Level 2 Proficiency). These data will be used to address the Primary Objective (see Section 2). In the last phase the patient is trained on autonomously switching the UNP system from 'stand-by' to 'on' mode and vice versa, without external help.

Frequency of visits by the research team will initially, during Phase 1 and 2, be maximally twice per week for at least 4 weeks, or until 28 weeks after implantation. During the first, second or third week only, depending on the condition of the patient, a maximum of 2 extra visits may be planned for training purposes, in order to quickly familiarize the patient with the system. Once a patient has entered phase 3, visits will initially occur once every 2 weeks, for 12 weeks. Subsequently, visits will occur once every 6 weeks until the end of the study. See Section 15.4A and B for examples of quick and slow scenario's. Notably, the actual scenario will depend on the individual patient's progress, and will probably be intermediate between the examples of Section 15.4. In addition, it may be necessary, when BCI performance suddenly decreases while being in a certain phase, to perform certain tasks from one of the previous phases. In that case, it will be made sure that the burden to the patient is not larger than originally planned.

Phase 1 - familiarization

The patient has two brain functions for controlling the device (control functions from here on) either by cognitive control and by motor imagery/attempt, or by different types of motor imagery/attempt. The function that showed the highest R^2 (as described in Section 8.3.7) is considered the primary control signal. The other function provides the secondary control signal. The patient will practice with both control signals. The patient is familiarized with controlling a computer with his thought (changes in brain activity). In this period a fine tuning of the device and the connected hardware is performed. These comprise the optimal frequency band or combination of frequency bands, the responsiveness of the system, i.e. how quickly a switch event is triggered, and the refractory period after a click, i.e. how quickly individual switch events can follow each other. Further the optimal threshold for eliciting a

switch event has to be identified. Phase 1 begins after the second surgery as soon as the patient's condition permits. Initially, the patient has to perform a 'Two Target Task'.

The Two Target Task is used extensively with the epilepsy grid patients. Training generally improves the performance over time and consequently patient confidence is increased. In this 1-dimensional two-target cursor control task the patient voluntarily modulates ECoG activity of the selected electrode pair in the specified frequency band to control the vertical movement of a cursor on a computer screen. The patient controls the cursor by engaging in the control function (to send the cursor up) or by relaxing (to send the cursor down). Each trial lasts 8.5 seconds and starts with an inter-trial interval (ITI) of 2.1 seconds, followed by the appearance of a target in the upper-right or lower-right corner of the computer screen (Target, vertical size 50% of screen height, horizontal size 10% of screen width). Next, a cursor appears (2.1 seconds after the target) and travels from left to right at a set pace (Cursor control, fixed travel-time of 2.3 seconds). The subject's task is to modulate the ECoG activity such that the cursor hits the target when it reaches the right edge. Correct hits are indicated by a color change of the target (Result); incorrect hits by an absence of color change.

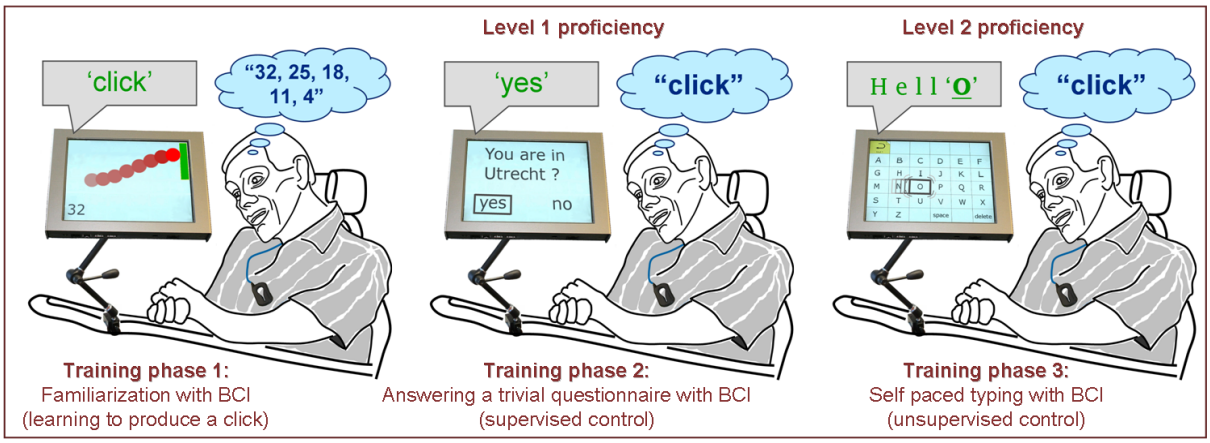

Figure 5. Training phases

Phase 2 - supervised BCI control

In phase 2 the patient will learn to use the switch(es) quickly and reliably. Along with the patient learning how to interact with the system, the system has to be calibrated according to the user's needs. The sensitivity and specificity of the system have to be maximized. The system calibration has to be done for each control signal as the dynamics of the neuronal processes at the implantation sites differ. In addition, the mental strategy used by the patient and the specific needs of the patient will influence these values. The patient is trained on a 'Click Target Task'. He has to activate the switch in response to a target on a screen. Targets (blue rectangle at the center of the screen) are presented for a limited period (starting with 10 seconds, decreasing throughout the training). As soon as the patient elicits a switch event, the target turns green and disappears after 1 second. The patient is then presented with a fixation cross for 5 to 10 seconds. If the target is clicked away in time this is counted as a hit,

otherwise it is counted as a miss; if the patient activates the switch during the inter trial interval this is counted as a false alarm. Depending on the progression of the training, the Click Target Task will be performed using the primary and/or the secondary control signal.

Once a week (starting from week 2, 3 or 4, depending on the postsurgical condition of the patient), a formal testing takes place (Level 1 proficiency), in which the patient has to perform the 'Communication Channel Verification Questionnaire' where he has to answer 20 questions with obvious yes/no answers (Section F1.3). These questions have to be answered using the BCI. In addition, the answers need to be detected each within a maximum period of 30 seconds. Each answer is obtained as follows: following presentation of the question, there are two consecutive 30-sec periods in which a brain signal can be generated by the patient, one period representing ‘yes’, the other ‘no’ (random order, indicated on a computer screen). If the patient wants to answer 'yes', he activates his BCI switch during the 'yes' phase and keeps it deactivated during the 'no' phase. Thus, each question lasts two times 30 seconds, and the total task lasts maximally 25 minutes (including time to actually state the questions). When 80% of the questions were answered correctly (with 50% being chance level) on two occasions, the patient is considered to have achieved significant supervised BCI switch control. The 80% correct criterion is based on two sources of information:

- A published user questionnaire (Huggins et al., 2011), where 50% of ALS patients with mixed degree of paralysis stated that they would be satisfied with a BCI device that performs at least at 80% hit rate.
- The unwritten standard in EEG BCI that BCI control is achieved at and above 70% correct responses in a BCI task (Viduarre et al., 2010), which we want to exceed.

When both dlpfc and motor strips are connected to the device, this process is first performed using the primary BCI control signal. The Research team may decide to repeat the phase two training procedure with the secondary control signal, or to switch to the secondary control signal if data suggest that this signal may yield better results. When two motor strips are connected to the device, supervised switch control may be investigated using several different electrode pairs and types of attempted movement. Training continues until the 'Communication Channel Verification Questionnaire' task criteria (a 80% score on two occasions/visits) are met with at least one of the control signals. Once the patient has achieved the set goal, phase 3 will start. We expect that reaching this first level of proficiency will take at least 4 weeks (Section 15.4 for examples of a quick and slow scenario). When the patient has not reached this level of proficiency within 28 weeks after implantation, the training will be discontinued and the patient will be excluded from further study (see Section 8.4).

Phase 3 - unsupervised BCI control

Once the patient is familiarized with the BCI control and can reliably control one or more basic switches in a supervised setting he starts the process of training to achieve unsupervised control of assistive technology. The focus will be on using the assistive technology device as a basic speller that the patient can use for communication. The

assistive technology the patient is equipped with (Touchy) provides the patient with scanning software. This software presents a keyboard on the screen; consecutively lines of letters are highlighted, when it is highlighted it can be selected by activating a single switch. Then the individual letters are highlighted for selection. By this method each letter of the alphabet can be selected by two activations of a single switch. The speed of the highlighting of the rows and columns depends on the speed the user can activate the switch with. Alternatively, if a patient had two strips over the sensorimotor cortex connected to the device and is able to control more than one switch reliably, the additional switch(es) can be used to increase speed of communication. A second switch can for example be used to change the direction of the highlighting (e.g. in case of a missed target), to quickly change to the next line, or for self-paced scanning (with highlighting of rows and columns each controlled with their own switch). When more than two switches can be controlled reliably, these may be used to for example move the highlighting up, down, left and right. During every visit, the patient will practice spelling using the scanning software.

The criterion for successful unsupervised BCI control (see Primary Objective, Section 2) will be if the system correctly detects a switch brain signal within 10 sec in a real-life cognitively engaging context, such as operating the abovementioned spelling device. The formal test is based on this criterion, and constitutes copying a 30 character sentence within 30 minutes, with a margin of maximally 20% faulty characters (Level 2 proficiency). Once a patient has entered phase 3 (after completion of phase 2, which we expect to occur between 4 and 28 weeks after implantation, Section 15.4 for a schedule), the patient is asked to copy this predefined sentence during every scheduled visit of the research team. Depending on the performance and condition of the patient the task may be terminated before the end of the sentence. Speed, number of letters spelled and number of errors is recorded. The task is recorded on video. On the basis of the results parameters of the BCI system can be adjusted to improve performance. Further, the patient will practice to produce his own sentences and to engage in a communication with the Research Team.

Once the patient has reached Level 2 proficiency, he has demonstrated that he can accurately control the BCI system using his brain signals. At this point, a possible request of the patient about using the UNP for environmental control (such as lights, television) will be considered by the research team. Conditions are that the device that will be controlled does not contain moving parts (e.g. door) and is not intended to generate temperature changes (e.g. electric blanket), and that the research team has approved the specific use and purpose.

Phase 4 – independent BCI control

The goal of phase 4 is to enable the patient to switch the UNP system from ‘standby’ to ‘on’ mode and vice versa without external help, through the generation of a key sequence with the switch. The standard mode of the system is the standby mode in which it does not react to the users command; this is to prevent false alarms. In this mode, however, the system does record and analyze brain activity. To activate the speller the patient has to produce a

specific pattern (key sequence) of switch events to unlock the system, similar to the pin code of a smartphone. The patient will be trained on generating this sequence using a Key Sequence Task. The sequence training is similar to the task used in phase 2. Here, the task however is more complex. The patient is again presented with a sequence of targets, but this time they are interleaved with non-targets. Targets and non-targets follow each other faster compared to the 'Click Target Task' with no interval between them in a fixed order. The patient has to activate the switch for the target and keep it deactivated for the non-targets. As soon as the patient can reliably produce the key sequence he can use the speller freely in the absence of the researcher. At this point the patient can make use of the UNP system to communicate with the researchers or care without any external help. The proficiency of switching the UNP system on and off will not be formally tested.

People involved

Research Team
Principal investigator

Responsibilities

The Research Team is responsible for BCI familiarization process.
The Research Team is responsible for administering the necessary tasks to fine-tune the switch parameters and choosing these parameters.
The Research Team is responsible for administering and evaluating 'Communication Channel Verification Questionnaire' task and the Copy Spelling Task of the predefined sentence to determine the level of BCI control.
The Principal investigator is responsible for the final decision regarding which BCI control channel to use as the primary channel.

8.3.10 Postsurgical Psychological Assessment

Executive summary

Throughout the study the patient has to perform 2 tests on a regular basis, to determine the quality of life of the patient, and how the quality of life is affected by the assistive technology. These tests will be performed during visits of the research team to the patient's home. The data are necessary to investigate secondary objective 1 (Section 2): to improve Quality of Life and user satisfaction. Additionally, during every visit the patient's motivation and mood is assessed using a VAS score.
In the case of unreliable communication at the time of inclusion, Quality of Life and user satisfaction questionnaires and mood and motivation assessment can only be conducted if the patient can use the UNP system to communicate reliably.

Full description of procedures

Throughout the study the patient has to perform 2 tests on a regular basis, to determine the quality of life of the patient, and how the quality of life is affected by the assistive technology. These tests will be performed during scheduled visits of the research team to the patient's

home (see Section 15.4). In addition, during every visit (e.g. those that are scheduled for BCI training and unscheduled visits for e.g. service to the system), the patient's motivation and mood is assessed using a VAS score. At the end of the study, the user satisfaction about the BCI device will be tested. All tests will be executed by a member of the research team.

Quality of Life

As part of addressing Secondary Objective 1 (Section 2), the quality of life will be assessed at the beginning (before implantation, see Section 8.3.1) and end of the study and four times in between in intervals of 12 weeks. The so called Anamnestic Comparative Self-Assessment (ACSA) will be used for this assessment, whose biographical +5 and -5 scale anchors the patient's memories of the best period in their life and their worst period ever. The test will take about 10 minutes to complete (Section F1.6).

The effects of the BCI on quality of life

As part of addressing Secondary Objective 1 (Section 2), the PIADS (Section F1.9) is used to estimate the effects of device on the quality of life. The test will be performed four weeks after the implantation and is repeated every 12 weeks until the end of the study.
PIADS (piads.net) is a 26-item, self-rating questionnaire that is designed to measure a person's perceptions of how assistive devices affect quality of life. The PIADS describes user experiences along three dimensions:
• Competence: Measures feelings of competence and usefulness.
• Adaptability: Signifies a willingness to try new things.
• Self-esteem: Indicates feelings of emotional wellbeing and happiness

Mood and Motivation

The mood and motivation of the patient will be assessed at the beginning of every visit (scheduled and unscheduled) using Visual Analogue Scales (Killgore 1999; Kleih et al., 2011, See Section F1.7). These data could be related to BCI performance, since this may be affected by mood and motivation.

User Satisfaction

As part of addressing Secondary Objective 1 (Section 2), user satisfaction will be measured during the last visit to the patient, using a dedicated questionnaire. The satisfaction with the BCI will be measured using a list of specific items, that will be rated by the patient on a four point scale that ranges from 'not satisfied at all' to 'very satisfied'. In addition, the opinion of the patient on the importance of each of these items will be assessed on a four point scale that ranges from 'not at all important' to 'very important' (See Section F1.8A+B).

People involved

Research team

Responsibilities

The research team will be responsible for planning and performing the tests.

8.3.11 Signal Data Collection for Research – Continuous Recording

Executive summary

This section describes the continuous 24/7 collection of data, which will take place during the complete period of use of the system by the patient, up until one year after implantation. These data are necessary to investigate Secondary Objective 1 (Section 2).

Full description of procedures

Data is collected throughout the study, 24 hours a day. Two types of data are collected, being the raw data from the Activa PC+S via the streaming unit, and logs of use of the UNP system. Both data are necessary to investigate the Secondary Objective 1 of the study (see Section 2). The Brain Interpreter receives and stores all data from the streaming unit continuously, including start time and parameter settings and including data from electrodes not used for control. This is handled by the source module of the Brain Interpreter software (see IMDD). A new file is opened every 24 hrs. The data format is the standard BCI2000 data file format (http://www.bci2000.org/wiki/index.php/Technical_Reference:BCI2000_File_Format). During standby mode, the data is also recorded, giving valuable information on behavior during a no control state. In addition to the raw data, the application module software records states and events, with a timestamp in the dat file and if necessary text logging in a separate ascii file. This ensures that data is labeled according to use by the patient, and on a detailed level during the key sequence.

States that are logged are:
- Idle (standby) or active (on) mode, activated by caretaker or patient

Events that are logged are:
- All events that are classified as an intent to use the switch, also in idle mode
- Caretaker starting or stopping active and idle mode
- Patient going in or out of idle mode.

Data is stored on the Brain Interpreters internal hard disk and during each scheduled visit of a member of the research team (see Section 15.4) it is copied to a mobile USB disk for backup. The Brain Interpreter deliberately has no internet connection to ensure data safety. The data will then be transferred to and stored on the server in the UMC Utrecht which houses the Library of all data of the research group. Data will be accessible and visible only to the members of the research team. Anonymized data can be made accessible through open-access libraries or through direct provision by the research team after written consent of the patient or his/her confidant. Data storage is described in Section 12.

People involved

Research team

Senior responsibilities
The research team will be responsible for data storage and database maintenance.

8.3.12 Signal Data Collection for Research – Task Data

Executive summary
This section describes the procedures for time based and frequency based data collection during scheduled visits. These data are necessary to optimize performance in using the BCI system for communication, because they can be used to adjust parameter setting.

Full description of procedures
Throughout the study, the patient will be visited on a regular basis by the research team (Section 15.4).The timing and frequency of the research data collection is independent of the progress of the training of the patient. During these visits, the patient will be asked to perform a number of rest and localizer tasks during which data is recorded in a dedicated fashion. For a description of the localizer tasks, see Section 8.3.7. During a rest task, the patient is asked to focus on a computer screen and think of nothing in particular, for 5 minutes. Signal will be recorded in time domain and frequency domain.

Signal data in the *frequency* domain are recorded during rest and during performance of the localizer task . For research on classifier stability over time the first data set will be used to train the classifier, the second to test the classifier. Signal data in the *time* domain are recorded also during rest and during performance of the localizer task . These data are used to optimize classifier algorithms and to assess effects of training on brain signal features.

Data is stored on the Brain Interpreter's internal hard disk and is frequently backed-up to a mobile USB disk. The data will then be transferred to and stored on the server that houses the Library of all data of the research group. Data will be accessible and visible only to the members of the research team. Anonymized data can be made accessible through open-access libraries or through direct provision by the research team after written consent of the patient or his/her confidant. Data storage is described in Section 12.

People involved
Research team

Senior responsibilities
The research team will be responsible for data storage and database maintenance.

8.3.13 Self-Practice and Home Use

Executive Summary
This section describes the possibilities for self-practice and home use of the system between visits of the research team.

Full description of procedures

Between visits of the research team, patients are allowed to use the system at any time they want for practice or real communication purposes. During phase 1 and 2 (see Section 8.3.9), patients can train using the feedback given by 4 LEDs on the minidisplay/keypad. During phase 3 and 4, also the assistive technology can be used. Using the buttons on the keypad, the caretaker will be able to switch on the system in the following modes for self-practice or home use:

- Idle mode (UNP system standby)
- Active mode (UNP system on)
- Feedback (Only keypad on, for practice)
    - Option 1 (signal): The number of LEDs switched on represents the brain signal strength: the higher the signal strength, the more LEDs will be switched on (fig 6A).
    - Option 2 (threshold): Two of the LEDs will be switched on when the signal is lower than the set threshold; the other two LEDs will be switched on when the signal is higher than the threshold (fig 6B).
    - Option 3 (key sequence): One of the LEDs switches between red and green. When the LED is green, the patient needs to increase brain activity, whereas he needs to relax and decrease brain activity when the LED is red. When brain activity follows the key sequence correctly, this will be indicated on the display of the keypad (fig 6C).

Figure 6A. The minidisplay while the UNP is in Feedback mode 1 (signal): it displays the power in the filtered signal with 1-4 LEDs.

Figure 6B. The minidisplay while the UNP is in Feedback mode 2 (threshold): it displays the outcome of the classifier (if 0 the lower LEDs are red, if 1 the upper LEDs are green).

Figure 6C. The minidisplay while the UNP is in Feedback mode 3 (key sequence): it displays the key sequence. The patient is informed if the key sequence was correct.

During phase 1 and 2, only feedback option 1 and 2 of the keypad may be used for practice. During phase 3 and 4, the caretaker may select to switch the UNP system in active ('on') mode, which will allow the patient to practice with the use of the assistive technology spelling device and/or to use the spelling device in real life. In addition, feedback option 3 may be selected, which will allow the patient to practice the specific key sequence that will eventually allow him to switch the UNP system on and off completely independently, without the help of the caretaker or research team. Notably, patients are not obliged to perform self-practice between visits of the research team, but are just offered the possibility.

People involved

Caretaker
Patient

8.3.14 Monitoring of cortical atrophy in case of long-term signal deterioration

Executive summary

This section describes the procedure in case the signal and/or BCI performance declines consistently for a longer time. In this case an additional CT scan and/or EEG measurement can be performed to assess the potential cause. The results of these measurements can be compared to the first CT scan and EEG measurement, respectively.

Full description of the procedures

When the signal or BCI performance declines over several months: 1) an additional hospital visit may be scheduled to conduct of a CT scan and 2) an additional EEG measurement may be made. The EEG measurement can be made at the participant's home or at the UMC Utrecht, depending on the wishes of the participant. The procedures for the acquisition of the CT scan are identical to those described under 8.3.7. This CT scan will be visually inspected and compared to the CT scan that was acquired at the start of the participants inclusion in the study. The inspection will focus on the distance between the electrodes and the cortical surface, which may enlarged as a result of for example disease-related atrophy, which may explain the decrease in signal amplitude and BCI performance. In case such gaps are detected, participant will be informed and end of participation will be discussed with the

participant, according to section 8.4.1. The signal quality and results of the additional EEG measurement will be compared to the signal quality of the first EEG measurement. A decline in signal quality of EEG signals might help to better understand the deterioration of the ECoG signals.

8.3.15 End of Study Participation

Executive Summary

This section describes in detail the possible end of study participation scenarios. They are applicable for all patients who have the Activa PC+S device implanted. The scenarios can be applied one year after the implantation of the device, at the end of an extended study participation and in cases where a subject is withdrawn from the study, by own choice or that of the legal guardian, or for medical reasons, or because of insufficient levels of proficiency at the 28-weeks evaluation moment or during extended participation (see also Section 8.4).

Full description of procedures

At the end of the study participation, one of five different scenarios may be followed. The choice of the scenario will be made by the patient (or legal guardian), in consultation with his/her confidant, the neurosurgeon and a psychologist. Before advising on these options, the neurosurgeon will take notice of all available safety information, both from the manufacturer and gathered in this study, including adverse events reported for the current or other patients, as well as the results (until that point in time) of the Clinical Follow-up.

1. All implanted parts will be removed surgically.
2. The subdural electrode strips and electrode leads will remain in place, the extension leads and the Activa PC+S device will be removed surgically.
3. The Activa PC+S device will be removed. The electrode leads and extension leads will remain in place.
4. All implanted parts remain in place and remain active. The Activa PC+S may be replaced by a similar device upon battery depletion. The choice of the device will depend on market availability. The battery of the Activa PC+S is expected to last for about 8 years after implantation.
5. All implanted parts will remain in place and are inactivated.

In scenario 1 a neurological examination will be conducted before and after the surgery, exactly similar as described for the first surgery in section 8.3.2.
In scenarios 2-5, one or more components will remain implanted after the end of the study participation. The parts that remain implanted are subject to Post Marketing Surveillance (PMS). PMS will be achieved through the involvement of Medtronic and the research team. The Permanent extensions, Activa PC + S and Antenna are subject to PMS by Medtronic. The subdural leads, both Resume II leads (model 3587A) and model 0913025 Subdural leads, are subject to PMS by the research team in the form of a Post-Market Clinical Follow-up (PMCF). In scenario 4, the Streaming Unit and Brain Interpreter Software will also be assessed in a PMCF study. The PMS plan is described in the IMDD (see Section D2). After

the end of study participation, the participants remain in the study to conduct the PMCF study (see Post Marketing Clinical FollowUp v2.0), consisting of a yearly questionnaire on adverse events, without further requirements for the patient. Adverse events will be registered as described in Chapter 9. The last informed consent before end of study participation remains valid during the PMCF period. Data obtained after the end of study participation will not be part of the final study report and are not monitored by the DSMB or monitor.
In case of medical costs that need to be made after the end of study participation, that are related to the implant, but not to damage due to study participation, it will be investigated if the health insurance of the participant or the sponsor of the study (UMC Utrecht) will reimburse these costs.

Surgery, scenario 1
The patient is subject to normal peri-operative procedures used at the department of neurosurgery at the University Medical Center Utrecht. Prior to surgery the patient will undergo a preoperative anaesthesiological screening. After completing one checklist (SURPASS, see Section 15.7) by the resident, one by the nurse and one by the neurosurgeon responsible for the procedure, the patient is transferred to the holding area of the OR center. An intra-venous canula is placed and connected to a Saline drip to prevent the canula from clotting. If the patient is on a ventilator he is transferred to the recovery area of the OR center. From there the patient is transferred to the operating theatre. The patient receives general anesthesia after completing the briefing and time-out procedure (SURPASS) with the anesthesiologist, neurosurgical scrub nurses and the neurosurgeon. As with all neurosurgical procedures 2 grams of cefazolin is prophylactically administered intravenously 30 minutes before skin incision.
The skin of the upper thoracic area and cranial areas containing the Activa PC+S, connectors and burr holes is disinfected with chlorhexidine and covered with Ioban. The skin incisions made during implantation are reopened. The skull fixation plates covering the leads of the electrode strips are removed. If necessary the burr holes are opened again by using a micro cutter. The subdural electrode strips are removed. The connectors of the extension leads are disconnected, and the extension leads are removed. The Activa PC+S is disconnected and removed. In case the neurosurgeon feels that the electrode strips cannot be removed safely, the leads will be cut. In that case, only the electrode strips will remain in place, and the primary electrode leads, extension leads and Activa PC+S will be removed as indicated above. All skin incisions are closed in two layers. The wound is covered by a patch and kept dry. The explanted materials are disposed of as infectious and hazardous medical waste according to European Waste Catalogue nr. 18 01 03.

Surgery, scenario 2
The patient is subject to normal peri-operative procedures used at the department of neurosurgery at the University Medical Center Utrecht. Prior to surgery the patient will undergo a preoperative anaesthesiological screening. After completing one checklist (SURPASS, see Section 15.7) by the resident, one by the nurse and one by the neurosurgeon responsible for the procedure, the patient is transferred to the holding area of

the OR center. An intra-venous canula is placed and connected to a Saline drip to prevent the canula from clotting. If the patient is on a ventilator he is transferred to the recovery area of the OR center. From there the patient is transferred to the operating theatre. The patient receives general anesthesia after completing the briefing and time-out procedure (SURPASS) with the anesthesiologist, neurosurgical scrub nurses and the neurosurgeon. As with all neurosurgical procedures 2 grams of cefazolin is prophylactically administered intravenously 30 minutes before skin incision.
The skin of the upper thoracic area containing the Activa PC+S and the temporoparietal area containing the connection between electrode leads and extension cables is disinfected with chlorhexidin and covered with Ioban. The linear temporoparietal skin incision made during implantation is re-opened. The electrode leads and the extension cables are disconnected, and the electrode leads are capped. The thoracic incision is re-opened and the Activa PC+S is disconnected from the two extension cables and removed. The extension cables are removed. The upper thoracic and cranial incisions are closed in two layers. The wounds are covered by a patch, and are kept dry. The explanted materials are disposed of as infectious and hazardous medical waste according to European Waste Catalogue nr. 18 01 03. The patient is prophylactically kept on cefazolin for two consecutive days.

Surgery, scenario 3
The patient is subject to normal peri-operative procedures used at the department of neurosurgery at the University Medical Center Utrecht. Prior to surgery the patient will undergo a preoperative anaesthesiological screening. After completing one checklist (SURPASS, see Section 15.7) by the resident, one by the nurse and one by the neurosurgeon responsible for the procedure, the patient is transferred to the holding area of the OR center. An intra-venous canula is placed and connected to a Saline drip to prevent the canula from clotting. If the patient is on a ventilator he is transferred to the recovery area of the OR center. From there the patient is transferred to the operating theatre. The patient receives general anesthesia after completing the briefing and time-out procedure (SURPASS) with the anesthesiologist, neurosurgical scrub nurses and the neurosurgeon. As with all neurosurgical procedures 2 grams of cefazolin is prophylactically administered intravenously 30 minutes before skin incision.
The skin of the upper thoracic area containing the Activa PC+S is disinfected with chlorhexidin and covered with Ioban. The thoracic skin incision is re-opened and the Activa PC+S is disconnected from the two extension cables and removed. The two extension cables are capped. The skin incision is closed in two layers. The wound is covered by a patch. The wound is kept dry. The explanted materials are disposed of as infectious and hazardous medical waste according to European Waste Catalogue nr. 18 01 03. The patient is prophylactically kept on cefazolin for two consecutive days.

Surgery, scenario 4
The patient is subject to normal peri-operative procedures used at the department of neurosurgery at the University Medical Center Utrecht. Prior to surgery the patient will undergo a preoperative anaesthesiological screening. After completing one checklist

(SURPASS, see Section 15.7) by the resident, one by the nurse and one by the neurosurgeon responsible for the procedure, the patient is transferred to the holding area of the OR center. An intra-venous canula is placed and connected to a Saline drip to prevent the canula from clotting. If the patient is on a ventilator he is transferred to the recovery area of the OR center. From there the patient is transferred to the operating theatre. The patient receives general anesthesia after completing the briefing and time-out procedure (SURPASS) with the anesthesiologist, neurosurgical scrub nurses and the neurosurgeon. As with all neurosurgical procedures 2 grams of cefazolin is prophylactically administered intravenously 30 minutes before skin incision.
The skin of the upper thoracic area containing the Activa PC+S is disinfected with chlorhexidin and covered with Ioban. The thoracic incision is re-opened and the Activa PC+S is disconnected from the two extension cables and removed. The new Activa PC+S is placed in the same surgical pocket and connected to the two extension leads and fixated. The skin incision is closed in two layers. The wound is covered by a patch. The wound is kept dry. The explanted materials are disposed of as infectious and hazardous medical waste according to European Waste Catalogue nr. 18 01 03. The patient is prophylactically kept on cefazolin for two consecutive days.

People involved
Anesthesiology Team
Neurosurgery Team
Research team

Responsibilities
The anesthesiologist is responsible for the anesthesiology related procedures. The neurosurgeon is responsible for the surgical procedure.

8.4 Withdrawal of individual subjects
Subjects can leave the study at any time for any reason if they (or their legal guardian) wish to do so without any consequences. If subjects wish to leave the study after the electrodes (subdural leads + extension leads) are implanted (first operation) they will be removed in a second surgery. If subjects wish to leave the study after the device (Activa PC+S) is implanted (second operation), the device will be disabled, and in consultation with the neurosurgeon, a careful choice will be made about explantation of (parts of) the implanted components.

The Principal Investigator can also decide to withdraw a subject from the study for urgent medical reasons, but only after consultation with the independent physician connected to the protocol. In cases of withdrawal for medical reasons, a careful choice will be made about explantation of (parts of) the implanted components, in consultation with the neurosurgeon.

8.4.1 Specific criteria for withdrawal (if applicable)

There are four evaluation moments when a subject can be withdrawn by the Principal Investigator.

The first withdrawal evaluation moment is before proceeding to admission to the hospital. The Principal Investigator can decide to withdraw a subject if his ability to perform the required tasks and / or his health is judged to be insufficient to partake in the study. The evaluation will be made based on the cognitive functioning, depressive symptoms and a health evaluation of the patient (see Sections 8.3.1 and 8.3.2).

The second withdrawal evaluation moment is after admission to the hospital, when the results of the fMRI scan have been evaluated. The Principal Investigator can decide to withdraw a subject if after two fMRI scans, no clear implantation spots can be identified based on the BOLD activation pattern (see Section 8.3.3), or if the fMRI scan reveals excessive cerebral atrophy.

The third withdrawal evaluation moment is before proceeding with the second surgery. The Principal Investigator can decide to withdraw a subject if no usable BCI channel can be determined (see Section 8.3.7).

The fourth withdrawal evaluation moment is at the planned six month evaluation moment following the second surgery (see Section 15.4). If the subject has not gained significant control of a BCI switch (see Section 8.3.9) at this time he will be withdrawn from the study.

In addition to these moments, the Principal Investigator may decide to withdraw a participant from the study when BCI performance no longer improves, despite significant efforts of the research team and the participant, and the benefits (for the project and the participant) of further participation no longer justify the burden and time investment. This decision may only be taken in the case of extended study participation (i.e. after at least one year of participation in the study).

8.5 Replacement of individual subjects after withdrawal

Withdrawn subjects are only replaced if withdrawn before the first electrode implant surgery.

8.6 Follow-up of subjects withdrawn from treatment

If patients are withdrawn from the study, their psychological wellbeing will be monitored as follows:

- 6 weeks and 12 weeks after withdrawal, the ADI-12 test (section F1.5) and Quality of Life test (ACSA, section F1.6) will be taken (only in the case of reliable communication)
- 12 weeks after withdrawal, we will schedule a concluding discussion with the caretakers and/or family.

The data obtained during these visits will be interpreted by the clinical neuropsychologist. If the neuropsychologist feels that the psychological wellbeing of the patient is endangered, an intake will be scheduled to the outpatient center Affective and psychotic disorders of the UMC Utrecht.

8.7 Premature termination of the study

If all of the first three participants fail to reach the first level of BCI performance, being supervised use (Section 8.1.1), within 6 months after implantation (Section 2), and convincing solutions for future participants cannot be conceived, we will consider terminating the study prematurely (in consultation with DSMB). In addition, if a serious adverse device effect is reported for two subjects, we will consider terminating the study prematurely (in consultation with the DSMB).

9. SAFETY REPORTING

9.1 Section 10 WMO event

In accordance to section 10, subsection 1, of the WMO, the investigator will inform the subjects and the reviewing accredited METC if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the accredited METC, except insofar as suspension would jeopardize the subjects' health. The investigator will take care that all subjects are kept informed.

9.2 AEs, SAEs and SUSARs

9.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the experimental intervention. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded. All adverse events related to the Medtronic products will be reported to Medtronic.

9.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that:

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity, other than the existing disability of the patient;
- is a congenital anomaly or birth defect;
- Any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered a serious adverse experience when, based upon appropriate medical judgement, the event may jeopardize the subject or may require an intervention to prevent one of the outcomes listed above.

All SAEs will be reported through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 15 days after the sponsor has first knowledge of the serious adverse reactions. SAEs will also be reported to the Clinical Representative of the funding agency (NIDCD).
SAEs that result in death or are life threatening should be reported expedited. The expedited reporting will occur not later than 7 days after the responsible investigator has first knowledge of the adverse reaction. This is for a preliminary report with another 8 days for completion of the report.
Notably, (scheduled) hospitalization for reasons of standard care and maintenance of invasive ventilation or other medical technology the participants may use will not be considered an SAE.

9.2.3 Serious Adverse Device Effects (SADEs)

Adverse device effects are all untoward and unintended responses to an investigational device.

Unexpected adverse device effects are SADEs if the following three conditions are met:

1. the event must be serious (see chapter 9.2.2);
2. there must be a certain degree of probability that the event is a harmful and an undesirable reaction to the medicinal device under investigation;
3. the adverse reaction must be unexpected, that is to say, the nature and severity of the adverse reaction are not in agreement with the device information as recorded in the IMDD.

The sponsor will report expedited the following SADEs through the web portal *ToetsingOnline* to the METC:

- SADEs that have arisen in the clinical trial that was assessed by the METC;
- SADEs that have arisen in other clinical trials with the same medical device, and that could have consequences for the safety of the subjects involved in the clinical trial that was assessed by the METC.

The remaining SADEs are recorded in an overview list (line-listing) that will be submitted once every half year to the METC. This line-listing provides an overview of all SADEs from the medical device, accompanied by a brief report highlighting the main points of concern. The expedited reporting of SADEs through the web portal ToetsingOnline is sufficient as notification to the competent authority.

The sponsor will report expedited all SADEs to the competent authorities in other Member States, according to the requirements of the Member States.

The expedited reporting will occur not later than 15 days after the sponsor has first knowledge of the adverse reactions. For fatal or life threatening cases the term will be maximal 7 days for a preliminary report with another 8 days for completion of the report.

9.3 Annual safety report

Not applicable (no investigational medicinal product).

9.4 Follow-up of adverse events

All adverse events will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

9.5 Data Safety Monitoring Board (DSMB)

A Data Safety Monitoring Board will be established for this study. It will perform online safety surveillance and performs interim analyses on the safety data. It will consist of a committee

whose members are independent from the research group. The DSMB will consist of experts in the areas of this research, including neurology, implantable devices and ethics.

The task of the DSMB will be to monitor the progress in the study in terms of achieving the stated objectives and improvement of the listed parameters for BCI signal processing. The DSMB meets before the study starts or early in the course of the study, to discuss the protocol, the study, any analysis plan, future meetings, and to have the opportunity to clarify any aspects with the principal investigators. After that, the DSMB will meet at least once a year. Additional meetings may be planned depending on timing of inclusion of patients and progress. One of the (regular or additional) meetings will be scheduled shortly after the first patient has been followed for six months after implantation. The DSMB will be asked to give advice at the decision moment after the third implantation, as to how to proceed based on the obtained results. It is the responsibility of the DSMB to verify adherence of the research team with the procedures as described in the research protocol.
The recommendations of the DSMB are circulated and approved by all DSMB members, then forwarded to the PI and, if deemed necessary, to the Ethics Committee of the UMC.

Criteria for decision to terminate the study prematurely

The key criterion for premature termination of the study (also stated in Sections 4.4, 8.7 and 10.4) is level of proficiency at 6 months after implant ('futility'). In addition the usual criteria are relevant, being unexpected problems with function of the device, unexpected systematic side effects that cause concern ('safety'). In addition the DSMB may decide to advise termination of the pilot study if results are above expectations (i.e. high levels of proficiency in all three first participants, 'positive efficacy'), to expedite a larger clinical trial.

9.6 Trial Management Group

In addition to the DSMB, a Trial Management Group (TMG) will be formed. The TMG comprises the key figures involved in the day to day running of the UNP project, including the principal investigator and other experts with detailed knowledge of BCI related topics. The TMG reviews and advises on the overall strategy of the UNP project. It meets regularly by teleconference of face-to-face meetings. The TMG advises on the strategic direction of UNP and recommends changes to take account of operational issues, acquired insights or developments in the field. The TMG's responsibilities include:
- reviewing the overall progress of the UNP study
- reporting to the DSMB
- reporting to the Medical Ethics Board

Proposed members are:
- Nick Ramsey (chair) (Dept neurosurgery, UMC Utrecht)
- Mariska van Steensel (Dept neurosurgery, UMC Utrecht)
- Erik Aarnoutse (Dept neurosurgery, UMC Utrecht)
- Peter van Rijen (Dept neurosurgery, UMC Utrecht)
- Peter Gosselaar (Dept neurosurgery, UMC Utrecht)

- Bon Verweij (Dept neurosurgery, UMC Utrecht)
- Gaetano Leogrande (Bakken Research Center, Medtronic, Heerlen)

10.STATISTICAL ANALYSIS

Given the fact that this is a pilot study preparing for a larger clinical trial, the statistical analyses for the endpoints are descriptive, and will be considered separately for each individual subject.

10.1 Primary study parameter(s)

Primary endpoint is proficiency of use of the BCI system. The research aims to evaluate performance of the BCI system at the start of implantation, and to then optimize performance. Two levels of profiency are formally tested on a regular basis.

First, the level of proficiency described as the primary objective, being *unsupervised BCI performance* (with the caregiver switching the UNP system from ‘on’ to standby’ mode and vice versa), with the criterion that the system correctly detects a switch brain signal within 10 sec in a real life, cognitively engaging context, such as operating a spelling device. The formal test is based on this criterion, and constitutes copying a 30 character sentence within 30 minutes, with a margin of maximally 20% faulty characters (Level 2 proficiency). Once a patient has entered phase 3 (after completion of phase 2, which we expect to occur between 4 and 28 weeks after implantation, Section 15.4 for a schedule), the patient is asked to copy this predefined sentence during every scheduled visit of the research team. Depending on the performance and condition of the patient the task may be terminated before the end of the sentence. Speed, number of letters spelled and number of errors is recorded. The task is recorded on video. Once the patient has reached Level 2 proficiency, he has demonstrated that he can accurately control the BCI system using his brain signals, and the UNP performance with the respective patient will be designated as successful. Success of the complete study is defined as: At least 50% of participants (3/5) reach level 2 proficiency and can thus communicate effectively as assessed with a formal test.

Second, we define a lower level of proficiency, which represents a level equivalent to that of the communication channel that the patient had before participation, being *supervised BCI performance*. In the case of unreliable communication at the time of inclusion, the lower level of proficiency constitutes reliable yes/no communication. Once a week (starting from week 2, 3 or 4, depending on the postsurgical condition of the patient), a formal testing takes place (Level 1 proficiency), in which the patient has to perform the 'Communication Channel Verification Questionnaire' where he has to answer 20 questions with obvious yes/no answers (Section F1.3). These questions have to be answered using the BCI. In addition, the answers need to be detected each within a maximum period of 30 seconds. Each answer is obtained as follows: following presentation of the question, there are two consecutive 30-sec periods in which a brain signal can be generated by the patient, one period representing ‘yes’, the other ‘no’ (random order, indicated on a computer screen). If the patient wants to answer 'yes', he activates his BCI switch during the 'yes' phase and keeps it deactivated during the 'no' phase. Thus, each question lasts two times 30 seconds, and the total task lasts maximally 25 minutes (including time to actually state the questions). When 80% of the

questions were answered correctly (with 50% being chance level) on two occasions, the patient is considered to have achieved significant supervised BCI switch control. Training continues until the 'Communication Channel Verification Questionnaire' task criteria (a 80% score on two occasions/visits) are met with at least one of the control signals. When the patient has not reached this level of proficiency within 28 weeks after implantation, the training will be discontinued and the patient will be excluded from further study (see Section 8.4).

10.2 Secondary study parameter(s)

Secondary study parameters are patient satisfaction and definition of a set of metrics for evaluation of efficacy of the BCI system for a larger clinical trial.
In the case of unreliable communication at the time of inclusion, secondary study parameters can only be investigated if the patient can use the UNP system to communicate reliably.

Patient satisfaction

This will be measured with standardized questionnaires and pattern of unsupervised use.

Quality of life

We assess the quality of life of the patient throughout the study. The so called Anamnestic Comparative Self-Assessment (ACSA) will be used for this assessment (Bruno et al., 2011), whose biographical +5 and -5 scale anchors the patient's memories of the best period in their life and their worst period ever. The first (presurgical) test serves as baseline measure. The test will be repeated five times after the implantation of the electrodes, in order to monitor whether quality of life changes over time (See Sections 15.4 and 8.3.10).

The effects of the BCI on quality of life

The PIADS (Section F1.9) is used to estimate the effects of device on the quality of life. PIADS (piads.net) is a 26-item, self-rating questionnaire that is designed to measure a person's perceptions of how assistive devices affect quality of life. For each of the 26 items, patients have to indicate (on a 7-point scale) whether this aspect of life has increased or decreased. The test will be performed four weeks after the implantation and is repeated every 12 weeks until the end of the study, in order to study changes over time.

Importance of Device Aspects and User Satisfaction

The opinion of the patient about the importance of a range of aspects of the device will be determined using a dedicated questionnaire. The patient will rate each item on a four point scale that ranges from 'not at all important' to 'very important' (See Section F1.8A). The test will be performed presurgically, and repeated at the end of the study to monitor any changes. At the end of the study, user satisfaction with the BCI will be measured using a list of specific items (the same items as in the 'Importance of Device Aspects questionnaire), that will be rated by the patient on a four point scale that ranges from 'not satisfied at all' to 'very satisfied' (See Section F1.8A+B).

Pattern of Use

The Brain Interpreter receives and stores all data from the streaming unit continuously, including start time and parameter settings and including data from electrodes not used for control.
States that are logged are:
- idle or active mode, activated by caretaker or patient

Events that are logged are:
- all events that are classified as an intent to use the switch, also in idle mode
- caretaker starting or stopping active and idle mode
- patient going in or out of idle mode.

Using this information, the number of times per day a patient uses the system for training or real communication will be determined, as well as the duration of each session.

Definition of a set of metrics for evaluation of efficacy of the BCI system for a larger clinical trial

Throughout the study, we will assess experimental parameters for a larger clinical study, including decoding algorithms, sample size, augmenting and prohibitive factors affecting BCI performance, factors affecting use of the system and indices of evaluation. This can only be investigated with chronically implanted systems, hence the present pilot study. All data collected during the visits of the research team to the patient can be used to assess these parameters. In addition, data acquired during the EEG measurement session will be used to address this study parameter. EEG data will be analyzed offline with standard programs for signal processing or custom programs. All data are converted to frequency space, and band pass filters are applied to generate multiple traces of power in specific bands (standard procedure). Of primary interest are theta (3-7 Hz) and mu/beta (7-28 Hz) bands. We will evaluate baseline spectral power as well as the ability of the participant to modulate power during the localizer tasks. Data will be compared with ECoG features and the fMRI activation pattern and will provide information about whether or not EEG measurements may be used to assess if certain individuals are more or less likely to generate high-amplitude changes in spectral power.

10.3 Other study parameters

fMRI activation pattern

fMRI data are analyzed with SPM8. The analysis parameters are the same as those that are used routinely for clinical fMRI data analysis as performed at the UMC. Briefly, fMRI scans are registered to the first scans, and then to the anatomical scan. Further analyses are performed in native space (not in a standard space such as MNI) so that the activity maps can be used during surgery. For the latter, the fMRI map superimposed on the native anatomy is co-registered with the patients head based on the fiducials or bone screws (see Section 8.3.3). For fMRI statistical analysis we use a General Linear Model multiple

regression analysis. The factor matrix includes a set of cosine waveforms acting as a high-pass filter to reduce random noise. The factors of interest depend on the task, but will correspond to the task designs, with brief (mental calculation) or standard epochs (motor imagery/attempt) corresponding to a block design. This method has been used in all the preceding research on intracranial BCI at the UMC Utrecht. Factor loadings (beta's) are converted to t-values, which make up the fMRI t-maps for each function (cognitive control, and motor imagery/attempt). Given our extensive experience with individual t-maps for clinical fMRI scans for neurosurgery, we will not apply a fixed cutoff for significance, but we will identify the peak t-values within predefined Regions of Interest. These are the border region between left hemisphere F1 and F2 (Brodmann areas 9 and 46) for cognitive control, and left premotor and motor region (Brodmann area 6 and 4) for motor imagery/attempt. Based on the patterns of activity around the peak values, the exact location and orientation of the 4 electrode strips is determined..

ECoG activation

ECoG data are analyzed with programs for signal processing or custom programs written in, for example Matlab, a platform for ECoG and fMRI research. Analysis involves offline and online processing. Offline processing is conducted for investigation of the full extent of data feature space to find optimal parameter settings for detecting brain activity. For this, tasks are imposed on the patient and correlations are sought between electrodes and tasks (similar to fMRI paradigms). First, data are converted to differential signals. Since the device can only create pairs within a strip, we have 6 possible pairs within each strip of 4 electrodes. Next, all data are converted to frequency space, and band pass filters are applied to generate multiple traces of power in specific bands (standard procedure). Next, for each trace the r-squared is calculated (similar to correlation value). Significant r-squares are then compared for low and high frequency bands. Of primary interest are theta (3-7 Hz) and gamma (50-100 Hz) bands for cognitive control, and mu/beta (7-28 Hz) and gamma (50-100Hz) bands for imagery/attempt, based on prior research, but specific frequencies are determined for each electrode pair and each individual separately based on r-squared values. Significance thresholds are $p<0.05$, Bonferroni-corrected for the number of electrode pairs (12 per function). During training, intention of the patient is detected using a linear summation of the signal features, followed by classification using a threshold. Finally, a machine learning algorithm is applied to the selected electrode pairs and frequency bands to build support vector machines for later online classification. Real-time ECoG data processing will not involve statistical testing. The selected frequency bands and electrode pairs are used, with classifiers that are based on the support vector machines determined in offline analyses. Classification is performed in real time, with parameter settings for conversion to a switch signal (Section 8.3.9).

10.4 Interim analysis (if applicable)

After three subjects the results are evaluated. Given that this is a pilot study, we will evaluate progress on an individual basis and make decisions on how to proceed based on achieved levels of BCI control. For details, see Section 4.4 and Section 8.7.

11.ETHICAL CONSIDERATIONS

11.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (version 7, October 2008) and in accordance with the Medical Research Involving Human Subjects Act (WMO) and relevant other guidelines, regulations and acts.

11.2 Recruitment and consent

11.2.1 Subject recruitment

Executive Summary

This procedure describes how we will reach possible patients, and how to go about once a patient has shown interest in the study.

Full description of procedures

Patients with locked-in syndrome who may be interested to be included in the BCI study will be identified as follows:

- Patient organizations, Assistive Technology companies, the 'Centrum voor Thuisbeademing', nursing homes, and other institutions and foundations will be approached by letter, with a request to inform potential candidates about the existence of the UNP project, and to provide potential candidates with the UNP information leaflet (see Section E3 for the letter sent to non-physicians).
- One month after these requests are sent out, it will be evaluated whether or not a sufficient number of eligible candidates could be found. If not, health care professionals of various disciplines (e.g. neurologists, general practitioners, rehabilitation doctors, physiotherapists) will be approached by letter with a request to inform the researchers whether or not they have locked-in patients in their practice or file. If they do, the professionals will be requested to approach the respective patients and their caregivers, and ask their permission for approach with information by the researchers (see Section E3 for the letter sent to professionals).
- A second letter will be sent out to "healthcare professionals" who didn't respond to the first letter.
- During the whole recruitment period, whenever possible, the UNP project will be presented by the researchers, e.g. during public outreach, interviews and scientific symposia.
- Four month after recruitment starts, if the number of eligible candidates is insufficient, we will extend recruitment and mention the possibility to participate in the UNP in more media, e.g. newsletters, websites and social media of patient organizations and other organizations related to our patient group. We will actively engage in social media for recruitment. In all of these media we will refer to the multilingual website set up for the UNP study: www.neuroprosthesis.eu (in English) / www.neuroprothese.nl (in Dutch). This website may be translated into other languages. See Section E3 for examples.

Patients/caregivers can contact the research team directly, or they can be contacted by the research team after caregivers have given agreement to their physician. Contact will be made with the patient or caregivers to confirm interest of the patient in the study and to verify that the patient meets inclusion criteria 1-8, and does not meet exclusion criteria 1-5 (see Section F1.1 and Section F1.2). The other inclusion/exclusion criteria will be thoroughly tested after the informed consent procedure. If the patient meets these first criteria, the patient will be visited by members of the research team, who will explain the project in detail. The complete project will be explained verbally to the patient and his/her relatives and/or caregivers and/or legal guardian. This information will include the following:

- the purpose of the research
- the expected duration of the subject's participation
- a description of the procedures to be followed and an identification of all the procedures which are considered experimental
- risks and benefits
- the extent to which confidentiality of records identifying the subject will be maintained

During this visit, the reliability of the patient's communication channel will be verified using a questionnaire (see Section F1.3 and F1.3b). When there is doubt about the patient's ability to communicate reliably the communication test can be repeated. When, the score is repeatedly below the criteria as described in section 11.2.2 the subject will not be included, unless there is evidence of earlier expressions of the will to participate after information was given to the patient (eg legal document).

A written summary of the research project will be provided by the investigator, as well as a letter in which they are formally asked to consider participation in the study (see Section E1.1). The patient is free to decide if he/she will participate in this study. Patients have 2 weeks to consider possible participation. In case of unreliable communication the legal guardian decides on behalf of the patient. The research team will make contact with the patient (or the family) after this period and ask whether the patient is still interested. If the patient is still interested, he will be once more visited by the research team and the project will be again explained verbally. During this visit, one of the neurosurgeons involved in the project will join the researchers. He will explain in detail the medical aspects of the procedure. For patients living abroad, this appointment may be accomplished via a video-call. ∗

After the explanation, the patient's understanding of the details of the project will be verified using a questionnaire (see Section F1.4). In case of unreliable communication this evaluation will not be possible with the patient, but it will be made sure that the legal representative is fully aware of all details of the study using the same questionnaire. This visit is followed by another, shorter, period of consideration about participation. A few days after this visit, the research team will have telephone contact with the patient (or family) to verify continuing interest in the study. If the patient remains interested and wants to participate, he/she will be visited by a member of the research team and an independent observer for the informed

consent procedure. For patients living abroad, the informed consent procedure will take place at the UMCU.

∗ For participants with an existing implant, the neurosurgeon will not join during this visit, since the patient will be aware of the medical issues related to the surgery. There will be a meeting with the neurosurgeon shortly before the implantation procedure.

If, during the process before the informed consent procedure, the researchers feel that the communicative abilities of the patient may benefit considerably from existing non-invasive assistive technology (e.g. commercially available dynamic systems, eye trackers etc) that he/she was not aware of before, the patient will be referred to an assistive technology advisor, see the Decision tree in Section 15.8. Considerations about possible inclusion in the current UNP study will be postponed until there is clarity about the alternatives.

In case of two eligible subjects at the same time, the date of the first contact between the patient and the researchers will determine who will be included first, with personal circumstances of the patient being taken into account.

People involved

Research team
Principal Investigator

Responsibilities

The research team will be responsible for contacting the patient and administering the telephone questionnaires. The principal investigator will be consulted once these questionnaires have been filled out, for a decision about inclusion or exclusion of the specific patient. The research team is also responsible for the explanation of the whole project to the patient, the verification of the reliability of the communication channel and the verification of the understanding of the project by the patient during the first visit to the patient. In the case of unreliable communication, the research team is responsible for determining if there is clear indication that the patient and legal guardian understand the protocol and the risks and want to participate (eg legal document), and if their legal guardian agrees to (and signs for) their participation.

11.2.2 Informed Consent

Executive Summary

This document describes in detail the informed consent procedure, including explanation of the project, testing of the reliability of the communication channel and the patient's understanding of the project.

Full description of procedures

Since patients will have a strong difficulty to communicate and will not be able to sign an informed consent form, the informed consent procedure will be recorded using a regular digital video camera. The acquired video file will be converted into at least 3 different formats (.avi, .mpeg and .mov), and those will be saved on DVD, as well as on our in house data server, which is backed up every day.

Besides the patient, three people will be present during the procedure: 1 confidant of the patient, 1 member of the research team and an independent observer. The informed consent procedure will involve the following steps:

- First, the best possible communication channel with the patient will be determined. Patients should at least be able to give clear responses by e.g. severely compromised speech, a switch, eye blinks etc.
- In order to test the reliability of the communication channel (most likely only a switch-like signal, such as an eye movement), 10 pairs of simple and irrelevant questions will be asked (see Section F1.3). Each of these questions will be followed by a yes and no option, to which patients may respond, making the number of possible choices 40. Patients need to select > 95% (=38/40) of these choices correctly, to be able to proceed with the rest of the informed consent procedure. In case of very subtle movements, we will repeat each question 2 times and take the majority (2/3 or 3/3) of the yes/no responses per question as the answer. Of these answers, 95% needs to be correct to proceed with the informed consent procedure.
- The complete project will be once more explained verbally to the patient and his/her relatives. This information will include the following:
    - the purpose of the research
    - the expected duration of the subject's participation
    - a description of the procedures to be followed and an identification of all the procedures which are considered experimental
    - risks and benefits
    - the extent to which confidentiality of records identifying the subject will be maintained
- The patient and his/her relative will be asked if they have any further questions. If yes, these questions will be answered.
- In order to verify that the patient has a full understanding of the procedure, a list of 10 questions about the project will be asked from the patient (see Section F1.4). When a question is answered incorrectly, the respective part of the protocol will be explained again to the subject.
- The last step will be asking the actual informed consent. The statements on the informed consent form will be read to the patient and the question about the willingness to participate in the project will be asked three times. Only if the answer of the patient is the same in all three occasions, the answer will be taken as convincing. If there is a discrepancy between the three given answers, the informed consent procedure will be repeated completely at another day. If the answer is ambiguous again, the subject will be excluded from the study (see Section E2).

- If the patient indicates he/she wants to participate in the study, the independent observer, as well as the confidant of the patient, will sign the informed consent form, thereby confirming that they believe that they are convinced that the subject has understood the information about the study, and has given voluntary consent to participate, via the available communication channel (independent observer and confidant), and that he agrees that the subject participates in the study (confidant) (see Section E2).
-

In the case of unreliable communication and earlier expression of the will to participate, the legal representative will sign the informed consent form after verification that the legal guardian understands the details of the study. A signature of an independent observer is not necessary in this case.

During the remainder of the study, each time data for research is collected (either in the hospital of at the patient's home), it will be asked whether the patient (or legal guardian) is willing to cooperate at that time point.

People involved

Research Team
Independent Observer

Responsibilities

The research team will be responsible for video-taping the whole procedure, the explanation of the project, the 2 questionnaires and the actual informed consent. The independent observer will observe the procedure and determines whether everything is executed according to the protocol, and that the answer to the actual consent question is interpreted correctly by the research team. If that is the case, he/she will sign the informed consent form as well to confirm these observations.
In the case of unreliable communication and previous expression of the will to participate, the legal representative will sign the informed consent form

11.3 Objection by minors or incapacitated subjects (if applicable)

All included subjects will be older than 18 years of age. Despite their condition, most included subjects are considered legally competent. We prefer to include patients who are able to give informed consent via their available communication channel. Prior to the informed consent procedure we determine whether the patient understands the protocol, and after informed consent we will perform a number of neuropsychological tests to verify that the patient is not cognitively impaired. We refer to Section 11.2 for an extensive description of the recruitment and informed consent procedure with these patients.
In the case of unreliable communication at the time of informed consent, evidence of earlier expressions of the will to participate after information was given to the patient (eg legal document) must be present, in which case the legal guardian will sign the informed consent form on behalf of the patient,

11.4 Benefits and risks assessment, group relatedness

11.4.1 General

The research is fully directed at the patient population participating in the study. The participating patients are likely to experience benefit from participation in terms of acquiring a new means of communication for the duration of the study. If the study succeeds in its objectives, it can provide patients with the means to engage in interaction with others and with their environment without the help of others, and at any time. This degree of autonomy is not available in any other way for these patients.

However, the research is high risk, in spite of the significant amount of proof-of-principle research leading up to this study, because there are no data from chronic implants yet that would allow us to estimate performance of the BCI system in real life. The current medical device is the first to be implanted for the purpose of BCI worldwide so there are no data to further strengthen the proof of principle research. There is a risk that the system fails due to unforeseen phenomena. Nevertheless, the prior research results strongly suggest that the experiment should work well in at least 50 % of the participants, and reasonably well in the other 50%, provided that electrodes are in the proper position (Vansteensel et al., 2010).
The participants will spend time in the UMC for the procedure, which involves two surgeries: one to position sets of electrodes and their leads, and one three days later to place the device and connect the leads. During their stay they undergo testing for determining the optimal electrode pairs for use, and start practising BCI with the signals. In case a participant already has ECoG electrodes and Activa PC+S implanted, one of the surgeries and the inter-surgery testing will not take place and its associated risks and burden do not apply. After recovery the patients go home and training continues until they can operate an AT device (Touchy). They continue to participate in research sessions aimed at obtaining performance measures, measures of use and satisfaction, and at improving the decoding technique to further improve performance (less error, faster switching). Hence the burden will be medical (surgical procedure), and devoting time and energy to the experiment. If the correct decoding of brain signals fails, and a patient is not able to gain accurate control over the BCI, this patient has no benefit of contributing to the study. If, however, correct decoding is successful, the benefit is possibly large, since he or she will have a new means of communicating with others and control of home environment.
After implantation, MRIs and the use of diathermia are no longer possible. If, during the study, an MRI is required for urgent medical reasons, the implanted parts need to be surgically removed before the scan.
Risks include those related to the fMRI scan, surgery, technical aspects of the device and emotional wellbeing. These risks are discussed below.

11.4.2 fMRI ∗

fMRI scanning is considered a safe procedure, and potential risks will be minimized by excluding patients who do not meet the inclusion/exclusion standards. Special care is taken to

ensure that the patient has no metal objects present in the body. Of particular concern are metal fragments in brain tissue or eyes, surgical clips and non-removable electronic devices, such as pacemakers.

Potential risks associated with the transport of a patient on artificial ventilation from the ICU to the MRI suite, and switching to the MRI compatible respiratory aid equipment in the MRI suite, are minimized by following the Standard Operation Procedure (see Section 8.3.3 and 15.1). The patient's vital signs such as heart rate, respiratory rate and oxygen saturation will be monitored continuously by the anesthesiology team. Furthermore, a member of the research team will be monitoring the available communication channel with the patient for the total duration of the fMRI scan. In the case of unreliable communication, this monitoring will not be possible possible and the vital signs of the patient will be informative about the patient's wellbeing. In consultation with the caretaker, one or more interruptions of the scan session may be scheduled for extra checkups and care if needed.

11.4.3 Surgery

The experiments involve a surgical procedure with implantation of electrodes underneath the skull, lead wires under the skin from the head to the chest, and/or positioning of a medical device under the skin on the chest. This procedure is the same as for deep-brain stimulators, but with a less invasive electrode positioning as they do not penetrate brain tissue (deep-brain stimulators travel through much of the brain white matter to reach their goal in the thalamus). Medtronic has already delivered 85.000 DBS stimulators for implantation in Parkinson patients alone, indicating that implantation of the device is by now a standard procedure.

∗ Because electrodes are already in place, imaging, electrode placement surgery and strip selection procedures are not relevant for new participants with existing implant.

The surgical implantation procedures (implantation of the electrodes and implantation of the Activa PC+S device) carry the same risks associated with any other brain surgery. In the worst case, risks of brain surgery may include serious complications such as coma, bleeding inside the brain, seizures and infection. Some of these may be fatal. However, the chance that complications occur is very low, among others since electrodes do not penetrate the cortex. The risk of subdural or epidural hemorrhage ranges from none to 2%. This literature is mostly based on devices penetrating the cortex (Bronstein et al., 2011; Franzini et al., 2011). Once implanted, the system may become infected. The risk of intracranial infection after implantation surgery is around 5% in the literature. The risk of infection at the abdomen where the cables are externalized is likely smaller.

Depending on the severity and the location of the infection, parts of the system may have to be explanted. After implantation, parts may wear through the skin, and the lead or lead/extension connector may move. Any of these situations may require additional surgery.

Notably, having two brain surgeries close together in time is standard clinical practice in the treatment of severe intractable epilepsy and other conditions, and does in itself not add any additional risks.

Risks related to the explantation scenarios (see Section 8.3.14) include infection (~3%) and, in the case of explantation of all implanted parts (including the electrodes), subdural or epidural hemorrhage (0-2%).

11.4.4 Technical aspects of the device

In case the UNP does not work (properly), or stops working after a period of good performance, the source of the problem has to be identified. There are a number of technical aspects or causes that need to be considered:

- The brain signal may show unexpected characteristics, making it an unreliable source of signals for UNP control. Based on our prior research with epilepsy patients we expect that the chance that this happens is very small, especially in the first period after surgery. The longterm effects of the use of a certain brain area for controlling the UNP on the characteristics of the measured signal is, however, presently unknown and one of the parameters investigated in the current study. Evidence from a recent study looking at action potentials indicates that five years after implant signals are still usable for BCI purposes (Hochberg et al. 2012). Regular system checks will give evidence on system integrity. If the characteristics of the primary control signal (see Section 8.3.9) prove to be too unreliable for correct UNP performance, we will switch to the secondary control signal and attempt to achieve UNP control using that.
- One of the external parts (outside the body) of the UNP is defective. In this case, the broken part may be repaired or replaced.
- One of the implanted parts of the UNP is defective.
    - Wire breakage of one of the leads. The chance that this happens is very small. Since the subdural leads are guided through the skull and led over the skull bone, they will not bend with handling the patient. The permanent extension leads that connect the primary leads to the Activa PC+S run subcutaneously through the neck area, which will be exposed to passive movements, e.g. during care or physical therapy. The permanent extension leads are, however, especially developed and CE marked to be placed in the head and neck region, and therefore have a minimal chance of breaking due to movement. Lead integrity tests are a feature of the Activa PC + S and can be run by Medtronic personnel. If a wire breakage occurs nevertheless, we will switch to the secondary control signal and attempt to achieve UNP control using that.

      The Activa PC+S stops functioning. If this happens, it will be investigated whether switching to the secondary control signal an option (e.g. if the problem in the Activa PC+S is related to a single channel only).

11.4.5 Emotional wellbeing

This study will inevitably have a large impact on the patient, not only practically, but also emotionally. Although it is made very clear in the information letter, and in conversation with the patient, that the UNP is an experimental device, and therefore may work less well than the patient expects, patients will gain hope of having an alternative or better communication channel. If the UNP does not work optimally, or stops working after a period of good performance, it will be difficult for the patient to stay motivated and for example try out alternative strategies, and there is a risk that the emotional wellbeing of the patient is endangered.
The psychological wellbeing of the patient will be monitored by 1) close contact with the patient, 2) speaking with the caretakers, 3) monitoring of the VAS scores for mood&motivation and 4) the psychological questionnaires that are carried out on a regular basis. The VAS scores and psychological questionnaires will be monitored by a clinical neuropsychologist of the UMC Utrecht, and the researchers will report their observations to her as well. If the neuropsychologist feels that the psychological wellbeing of the patient is endangered, an intake will be scheduled to the outpatient center Affective and psychotic disorders of the UMC Utrecht.
In the case of unreliable communication, these assessments can only be conducted if the patient can use the UNP system to communicate reliably. Emotional wellbeing will be assessed in consultation with the primary caregiver and the legal guardian.

11.4.6 CT scan and X-ray ∗

Each brain CT-scan will expose the participant to 2 mSv of ionizing radiation. There is a very small increased risk of 0.01% a participant develops a fatal cancer as result of this study. Each additional X-ray for verification of MRI compatibility will add an exposure of 0.04 mSv or less, with negligible extra risk for the patient.

∗ Because electrodes are already in place, imaging, electrode placement surgery and strip selection procedures are not relevant for new participants with existing implant.

11.4.7 Bone screw placement ∗

Bone screw fiducials are known to produce higher neuronavigation accuracy than skin fiducials (Thompson et al., 2011), and, more importantly, have the additional advantage (compared to skin fiducials) that re-registration can be performed during surgery, in cases a patient, skull-clamp or reference frame drifts away from its original position (Stieglitz et al., 2013). The technique involves local anesthesia of the scalp, making small scalp incisions and placing dedicated bone screws. A potential risk is associated with placement of screws in areas where the underlying bone is thin or absent.
Abnormal bone thickness or absence of bone will however become clear during the preparatory steps (fMRI, skin incision, drilling of small hole in the skull) before the placement of the screws. Also, there is a potential risk of infection which can be avoided by careful skin

disinfection (Stieglitz et al., 2015). Therefore, the risk of bone screw placement can be considered minimal.

11.4.8 EEG meaurements

There are no known risks associated with EEG acquisition.

11.4.9 Device expiration

New Activa PC+S devices are no longer produced by Medtronic. The expiration date of the remaining Activa PC+S devices is April 28 2020. We have determined that the sterility of devices is not negatively impacted if the devices are implanted within six months after the expiration date and that the six-month additional time period beyond the expiration date has minimal effects on the battery life (1-1.5% reduction of the original battery life, i.e. of an expected 8 years). Medtronic will continue delivering technical support until the end of the study for all devices used in the study, including the Activa PC+S devices implanted between April 28 and October 29 2020.

∗ Because electrodes are already in place, imaging, electrode placement surgery and strip selection procedures are not relevant for new participants with existing implant.

11.5 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7, subsection 6 of the WMO.

The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO and the Measure regarding Compulsory Insurance for Clinical Research in Humans of 23th June 2003). This insurance provides cover for damage to research subjects through injury or death caused by the study.
€ 450.000, -- (i.e. four hundred and fifty thousand Euro) for death or injury for each subject who participates in the Research;
€ 3.500.000, -- (i.e. three million five hundred thousand Euro) for death or injury for all subjects who participate in the Research;
€ 5.000.000,-- (i.e. five million Euro) for the total damage incurred by the organization for all damage disclosed by scientific research for the Sponsor as ‘verrichter’ in the meaning of said Act in each year of insurance coverage.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

For study procedures conducted abroad, a local insurance is in place.

11.6 Incentives (if applicable)

Not applicable. All medical costs and travel costs related to the project will be covered, however.

12.ADMINISTRATIVE ASPECTS AND PUBLICATION

12.1 Handling and storage of data and documents

Data are coded to maintain privacy. All data files are stored with a code (UNP001 to UNP005) to secure anonymity. The research team will unavoidably be aware of the subject's identity (all will work intensively with the participants). Identity will be kept within the research team at all times. No identifiable information will be shared when data are made publicly available through open-access libraries or through direct provision by the research team. No data will be shared if participant did not give consent.

12.2 Monitoring and Quality Assurance

The monitoring plan is provided separately (section K6).

12.3 Amendments

Amendments are changes made to the research after a favorable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favorable opinion.

12.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

12.5 End of study report

The investigator will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last research data collection from the last patient.

In case the study is ended prematurely, the investigator will notify the accredited METC, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

12.6 Public disclosure and publication policy

Data will be published in national and international peer-reviewed journals, with data anonymized.

Upon the request of Medtronic, anonymized clinical data and/or study results will be made available to Medtronic. Data will be processed, transferred and stored in a secure cloud storage platform or other secure data transmission method.
For various reasons (e.g. journal's requirements, general support or competitions) the research team will give public access to anonymized (clinical) data and/or study results after the written consent of the participant or his/her confidant.

13.STRUCTURED RISK ANALYSIS

13.1 Potential issues of concern

a. Level of knowledge about mechanism of action

A BCI is based on the principle that people can consciously and voluntarily change the activity of certain brain regions, which can be translated into commands that control a device. Extensive work performed in the last 4 years in our lab has focused on critical parameters for intracranial BCI. The critical parameters are: where to place electrodes (brain function and region), what signal features to utilize and what to use as a reference for the signal.
The best electrode target region for BCI proved to be the dorsolateral prefrontal cortex. This region works well in every epilepsy patient who had electrodes placed there as evidenced by an extensive study we conducted recently (Vansteensel et al., 2010, Ramsey et al., 2006). Moreover, false positive rate can be kept quite low (Torres Valderrama et al., 2012).
The other target region will be the motor system. Premotor areas have been demonstrated to become activated upon imagery of motor movements (Hermes et al., 2011b), and there is evidence that paralyzed patients can additionally attempt to make movements, which may activate the primary motor cortex as well (Hotz-Boendermakers et al., 2008).
For both functions, frequencies between 65 and 95 Hz were specifically usable for BCI control. For WM, BCI performance using bipolar signals was comparable to levels attained using unipolar signals (see also Section 15.5, and D2, Annex VIII).

b. Previous exposure of human beings with the test product(s) and/or products with a similar biological mechanism

As written in D2 (IMDD, Section 2, and the documents mentioned therein), previous versions of the Activa PC+S and the Patient Programmer exist.
Using the current version of the Activa PC+S, we conducted safety tests, which were all passed. Performance of the complete system was verified in several stages;

- Test safe connection of device to clinical Micromed intracranial EEG system
- Test device performance with subdural signal
- Test controllability of ECoG brain signal
- Test wireless implantable device outside body with noise data
- Test wireless implantable device outside body with EEG

From these tests, it was concluded that performance using the Activa PC + S, also with telemetry, is similar to performance with the clinical system. Details are given in D2 (IMDD)

c. Can the primary or secondary mechanism be induced in animals and/or in ex-vivo human cell material?

Yes, the use of ECoG brain signals of the motor cortex for closed loop BCI control has been demonstrated using non-human primates (Rouse et al., 2011)

d. Selectivity of the mechanism to target tissue in animals and/or human beings

Whereas it has been demonstrated that non-human primates can use brain signals, recorded from the motor cortex using ECoG electrodes, to control a cursor task on a computer screen (Rouse et al., 2011), the use of working memory related function and brain areas cannot be tested using animal studies, since animals cannot perform a mental calculation task. Moreover, important differences exist between animals and humans in terms of size and exact location of the relevant brain areas, as well as in the spectral power characteristics of their brain signals. The animal studies have been superseded by the human studies performed in the UMC Utrecht (see also D2, IMDD).

e. Analysis of potential effect

As described in D2 (IMDD, Annex VIII) we investigated whether ECoG signals can be used to control a switch in two epilepsy patients. The 'clicks' generated are the input for an assistive technology device, that uses these clicks to select letters in a matrix. We demonstrated that a brain-controlled switch can be used successfully as input to an assistive device for communication. Speed was on average 21.5 s per letter, and although there were some misses and false alarms, there were no incorrect letters selected.

f. Pharmacokinetic considerations

N.A.

g. Study population

The study population consists of patients of age 18–75 years who are in a locked-in state. The severity of the disability is essential for inclusion, not the cause (could be stroke, high spinal cord lesion, neuromuscular disease etc). Only patients in a medically stable condition will be considered.

Inclusion requirements include ~~availability of at least one means of communication,~~ mental capacities intact, stable psychological condition, and good medical health. See Section 4.

h. Interaction with other products

As written in Section 11.4, MRIs and the use of diathermia are no longer possible after implantation. If, during the study, an MRI is required for urgent medical reasons, the implanted parts need to be surgically removed before the scan.

i. Predictability of effect

As described in Section 15.5 and D2 (IMDD, Annex II and Section 1.8.6), we have demonstrated that:

- fMRI is a suitable technique to predict the brain areas that give the largest effects in ECoG recordings, including BCI control tasks, and that therefore can be designated as target coordinates for the electrode-strip implants
- the results of localizer tasks during ECoG recordings can be used, together with the fMRI data, to select the optimal electrode pair and frequency band of interest, for subsequent use in BCI control.

j. Can effects be managed?

In the course of the training schedule (see Section 8.3.9) the functioning of the BCI system will be optimized (maximizing true positive rates, minimizing false positive rates) by adjusting parameters on the level of feature selection, classification and/ or translation, see D2 (IMDD).

The effects will additionally be managed by initially limiting the use of the BCI system to make selections on a computer screen, and to writing text. This will be necessary, since we do not yet know how proficient participants can operate the BCI system and the ability to switch home devices on or off may not be safe. In the course of the study (once patients have reached a certain level of proficiency), the possibility of environmental control (e.g. tv, lights) may be made available to the patient. Conditions will in that case be that the device that will be controlled does not contain moving parts (e.g. door) and is not intended to generate temperature changes (e.g. electric blanket), and that the research team has approved the specific use and purpose. See also Annex II of the IMDD (D2-AnnexII-Instructies Utrecht NeuroProthese).

13.2 Synthesis

For an overview about the measures that have been taken to reduce risks, see D2 (IMDD, Annex VI). We consider the remaining risks acceptable for the study population, since the participating patients are likely to experience benefit from participation in terms of acquiring a new means of communication for the duration of the study. Remaining uncertainty is that there are no data from chronic implants yet that would allow us to estimate performance of the BCI system in real life. Therefore, the actual benefit for each individual is hard to estimate, and is actually part of the research of this study.

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15.APPENDICES

15.1 fMRI Standard Operating Procedure

Executive summary

This Standard Operating Procedure (SOP) has been designed to support the research team of the UNP project in the safe and correct execution of the study protocol, part 'fMRI scan'. It describes step-by-step the procedure of transporting a patient on artificial ventilation from the Intensive Care Unit (ICU) to the MRI scanner room, then to the MRI trolley and finally the return to the ICU. Of particular importance during this procedure is the safe continuation of the respiratory aid of the patient. The SOP has to be completed entirely at all times. If something is unclear, contact the principal investigator.

Full description of procedures

TIMELINE

Team Briefing

In a team briefing, the research team and the ICU team will receive a detailed explanation about the procedure by the study coordinator. During this briefing, the communicative abilities of the patient will be discussed explicitly. The procedure is started when the briefing is completed.

fMRI procedure

T −120 min — A member of the neurosurgery team visits the patient to place the fiduciairy markers.
The research team visits the patient to explain the fMRI procedure, repeat the task practice and, if necessary, prepare MRI compatible glasses. The team completes the
-Checklist visite onderzoekers

T−75 min — The ICU team sets up the ventilator, monitoring and registration devices in the MRI suite. New ventilator tubing is used for each patient. The team completes the
- Checklist Protocol voor gebruik van Anesthesietoestel in MR-ruimte.
- Checklist Setup Aestiva anesthesietoestel.

T−45 min — The ICU team prepares the patient for transport to the MRI scanner. The patient receives MRI compatible clothing. All non-MRI-compatible objects are removed from the patient. The team completes the following checklists:
-Checklist voor vertrek naar MRI
-Checklist transportkar voor vertrek naar MRI

T−25 min	The ICU team transports the patient to the MRI suite
T−20 min	Arrival at MRI suite. Radiology team checks the MRI screening form (see Section F1.2). The patient will be transferred from his bed to the MRI trolley using the PatSlide, and switched over to the MRI compatible ventilator, monitoring and registration devices. Monitoring and registration adhere to hospital protocol and American Society of Anesthesiologists (ASA) minimal monitoring standards and consist of 3-lead ECG, pulseoximetry, non-invasive bloodpressure and capnography.
T−5 min	The patient will be positioned in the scanner by the radiology team and ICU team. If applicable, an eye tracker will be installed by the research team to facilitate communication with the patient.
T0 min	Scanning starts. A member of the ICU team stays in the scanner room with the patient to observe the clinical condition, provide airway suctioning and, if necessary, administer medication. The flowmanager operates the scanner. The research team operates the fMRI computer, and checks the communication channel of the patient.
T60 min	Scanning completed. The radiology team and ICU team take the patient out of the scanner room, transfer the patient back to ICU transport monitor and ventilator, and finally transfer the patient from the MRI trolley back into the ICU bed.
T75 min	Time Out before departure to the ICU. The ICU team transports the patient back to the ICU, reconnects ICUventilator, monitoring and registration devices. The team completes the -*Checklist bij terugkomst IC*
T90 min	The ICU team hands the patient over to the ICU staff as per standard ICU practice. The studycoordinator collects all checklists, and calls a team debriefing when complications have occurred, or any team member wishes to debrief the procedure.

End of the fMRI Procedure

People involved

Research team / principle investigator
Research team / studycoordinator
Medical team/ Intensive Care Unit (ICU) team
Medical Team/ Radiology team

15.2 fMRI Standard Operating Procedure (Checklists)

Checklist Study coordinator

		Ochtend
Inform IC staff	□	
Team Briefing	□	
Onderzoekersteam: Checklist visite onderzoekers	□	
		2 uur voor scan
IC Team: anesthesietoestel gereed bij MRI?	□	
IC Team: Transportkar gereed op IC?	□	
IC Team: Checklist voor vertrek naar MRI	□	
IC Team: Checklist transportkar voor vertrek naar MRI	□	
MRI bellen (56085)	□	
		Na scan
IC Team: Checklist bij terugkomst IC	□	
IC Team: Zorg overgedragen aan IC personeel?	□	
IC Team: Transportkar opgeruimd?	□	
IC Team: Anesthesietoestel opgeruimd?	□	
Debriefing	□	

Checklist volledig | Datum:……..|Tijd:……|Paraaf:……

Checklist visite onderzoekers (Research Team)

Meenemen naar patient:

Oefen laptop	□
Zo nodig: MRI bril + glazen	□

fMRI procedure duidelijk	□
Taken geoefend en duidelijk	□
Zo nodig: MRI bril afgesteld	□

Checklist volledig | Datum:……..|Tijd:……|Paraaf:……

Checklist voor vertrek naar MRI (ICU team)

A	Airway	□			
B	Beademingsvoorwaarden	□	AMV:	SpO2:	etCO2:
C	Hemodynamiek	□	RR:	MAP:	P:
D	Patient begrijpt procedure	□			
	MRI-compatibele kleding	□			
	Metalen in / op lichaam	□			

Meenemen:

Midazolam	□
Efedrine	□
Rocuronium	□
Fenylefrine (50 ml)	□
Patientenstatus	□
Communicatie-hulpmiddelen	□

Checklist volledig | Datum:……..|Tijd:……|Paraaf:……

Checklist transportkar voor vertrek naar MRI (ICU team)

A	Flowsensor/Capnograaf	□	
	Zuurstof fles > 100 bar OPEN	□	
	Perslucht fles > 100 bar OPEN	□	
	Zuigdrainage artikelen	□	
B	Beademingsinstellingen	□	
	Alarmen beademing ingesteld	□	
C	Alarmen monitor ingesteld	□	
	MRI ECG stickers	□	

	MRI gebeld	□	

Checklist volledig | Datum:……..|Tijd:……|Paraaf:……

Protocol voor gebruik van Anesthesietoestel in MR-ruimte

- Controleer **alvorens** het gebruik IN de MR-scannerruimte;

. Of het toestel geschikt is voor gebruik in een MR-ruimte, dit is aan gegeven met een van de onderstaande symbolen (evt. zonder tekst);

MR-safe
MR-veilig

MR-safe
MR-veilig

MR-conditional MR-safe
MR-conditioneel MR-veilig

. Of het toestel goed functioneert buiten de MR-ruimte;

. Het gemonteerde touw niet beschadigd is, nog goed vastzit aan het toestel en voorzien van een deugdelijke afsluitbare haak. Neem bij twijfel contact op met het Technisch Cluster Divisie Beeld, tel 57000;

- Controleer **IN** de MR-scannerruimte of het bevestigings-oog nog goed vastzit aan de wand (onder het raam). Zo niet neem dan contact op met het Technisch Cluster Divisie Beeld, tel. 57000.
- Bevestig vervolgens **EERST** het touw met de haak aan het bevestigings-oog.
- Rijd **daarna** pas het toestel naar de gewenste plaats, echter **NIET** dichterbij de magneetvoorkant dan **1,5 meter** in geval van gebruikt bij een 3 Tesla MR (MR7 en MR8).
- Maak vervolgens het toestel gebruiksklaar.

Neem bij vragen en/of twijfel contact op met het Technisch Cluster Divisie Beeld, tel 57000;

Checklist Aestiva

1. Controleer het systeem op compleetheid
   - Sluit de absorber
   - Vulling en conditie sodalime
   - Plaatsing verdampers
   - Verwijder eventueel water uit slangen en sodalime reservoir

2. Zet de Aestiva aan: let op dat de O2-uitlezing op de display 21% is
   - Voer de O_2 sensortest uit (geef 2 min 100% O_2, de sensor moet 100% aangeven)
   - Calibreer de O_2 cel zonodig

3. Controleer
   - Gasdrukken van het centraal net en O_2 cilinder
   - Link 25 systeem, flowmeters O_2, Air en N_2O (let op toestel niet aan: geen flow over het rotameterblok)
   - O_2 bypass
   - Excretie afzuigsysteem

4. Lektest handbeademing
   - Zet APL klep dicht (70 cm H2O)
   - Sluit inspiratoire deel coaxiale beademingsysteem af met rode plug
   - Vul het systeem met de O_2 flush tot 30-40 cm H_2O
   - De druk is afleesbaar op de manometer en moet constant blijven
   - Sluit expiratoire deel coaxiale beademingsysteem af op de Aestiva (boven front-outlet)
   - Vul het systeem met de O_2 flush tot 30-40 cm H_2O
   - De druk is afleesbaar op de manometer en moet constant blijven

5. Lektest ventilatorbeademing
   - Slagvolume 500ml, frequentie x 12x/min, I/E ratio 1:2
   - Luchtwegbegrenzing (P-limiet) 40cm H_2O
   - Sluit Y-stuk af
   - Vulling van de balg met O_2-flush knop
   - Schakel de ventilator in met schakelaar van hand naar mechanische beademing
   - Beademing zal niet boven 40cm H_2O komen en de balg keert boven in de behuizing terug na ieder inspiratie
   - Stel na de test de gewenste instellingen in

6. Aan het einde van het programma
   - Open de absorber
   - Vervang zonodig verzadigd sodalime op indicatie
   - Indien erg veel vocht: laat de O_2 cel in de buitenlucht drogen

Checklist bij terugkomst IC (ICU team)

A	Tube gezekerd	□	
B	Beademingsinstellingen	□	
	Alarmen beademing ingesteld	□	
C	Saturatie in beeld	□	
	Bloeddruk in beeld	□	
	CVD in beeld	□	
	ECG in beeld/nieuwe plakkers	□	
	Alarmen monitor ingesteld	□	
	Alle pompen weer gestart	□	
D	Communicatie-hulpmiddelen	□	

Checklist volledig | Datum:……..|Tijd:……|Paraaf:……

15.3 Placement Skin Fiducials

PROTOCOL: AANBRENGEN VAN HUID FIDUCIALS tbv
NEURONAVIGATIE OK's

AUTEUR: PA Woerdeman
EINDVERANTWOORDELIJKE: Dr J.W. Berkelbach vd Sprenkel

DATUM(nieuwste versie): 01- 09-2011

TREFWOORDEN: frameloze neuronavigatie, huid fiducials

OMSCHRIJVING: aanbrengen van huid fiducials op het hoofd tbv frameloze neuronavigatie

DOEL: goed aanbrengen van huid fiducials op het hoofd tbv frameloze neuronavigatie

Indicaties:
- CT en MRI geleide neurochirurgie met gebruikmaking van de TREON navigatie apparatuur

Soort fiducial plakkers:
- Fiduciary markers (Medtronic Navigation, Boulder, CO - USA), gemaakt door IZI Medical Products Corporation

Benodigdheden:
- wegwerp scheermesje
- gaasjes
- ether
- markerings stift
- lege, nieuwe CD-rom

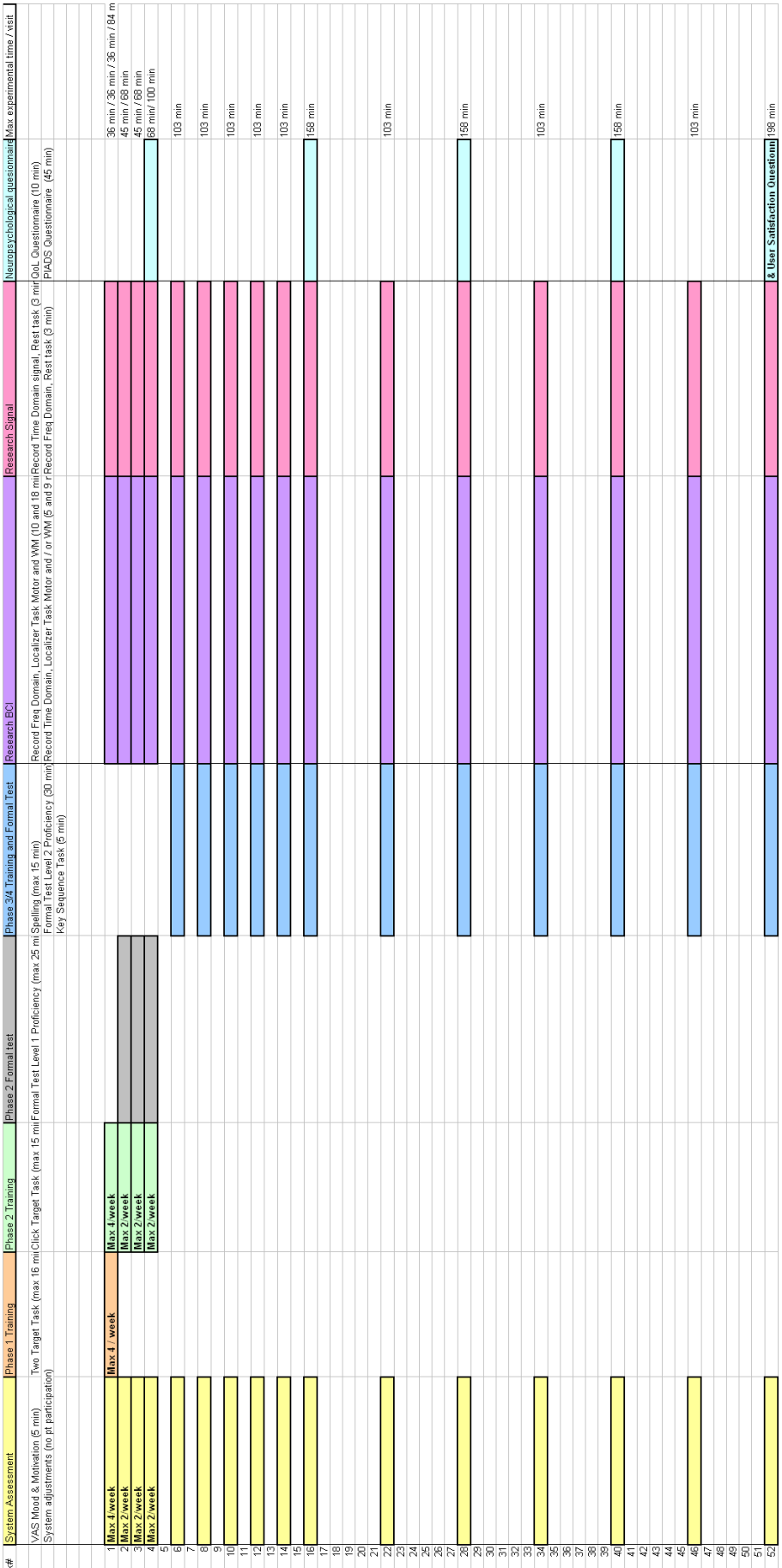
Uitvoering: (zie ook figuren hieronder)
1. Scheer wat haar weg ter plekke van de geplande fiducial lokatie.
   - Supratentorieel: als figuur 1, tumorzijde bepaalt welke mastoid zijde beplakt dient te worden. NB: Zorg er dus voor dat aan de zijde van de tumorlokatie de fiducidal op het mastoïd geplakt wordt. Zo wordt een asymetrische plakkerverdeling verkregen en voorkomt een eventuele rechts – links verwisseling in het navigatisysteem ten tijde van de "patiënt –to – image" registratie.
   - Infratentorieel: als figuur 2.
     NB. Zorg ervoor dat de fiducials niet/zo min mogelijk ten tijde van scanning ingedrukt kunnen worden in deze liggende positie.
2. Ontvet de huid met wat ether
3. Haal fiducial van het ronde stickervelletje en zorg dat er in het midden van de fiducial ge geen plastic zit.
4. Plak de fiducial op de huid
5. Omcirkel de fiducial en maak een midden-markering met de markeringsstift

15.4 Post Implantation Time Line

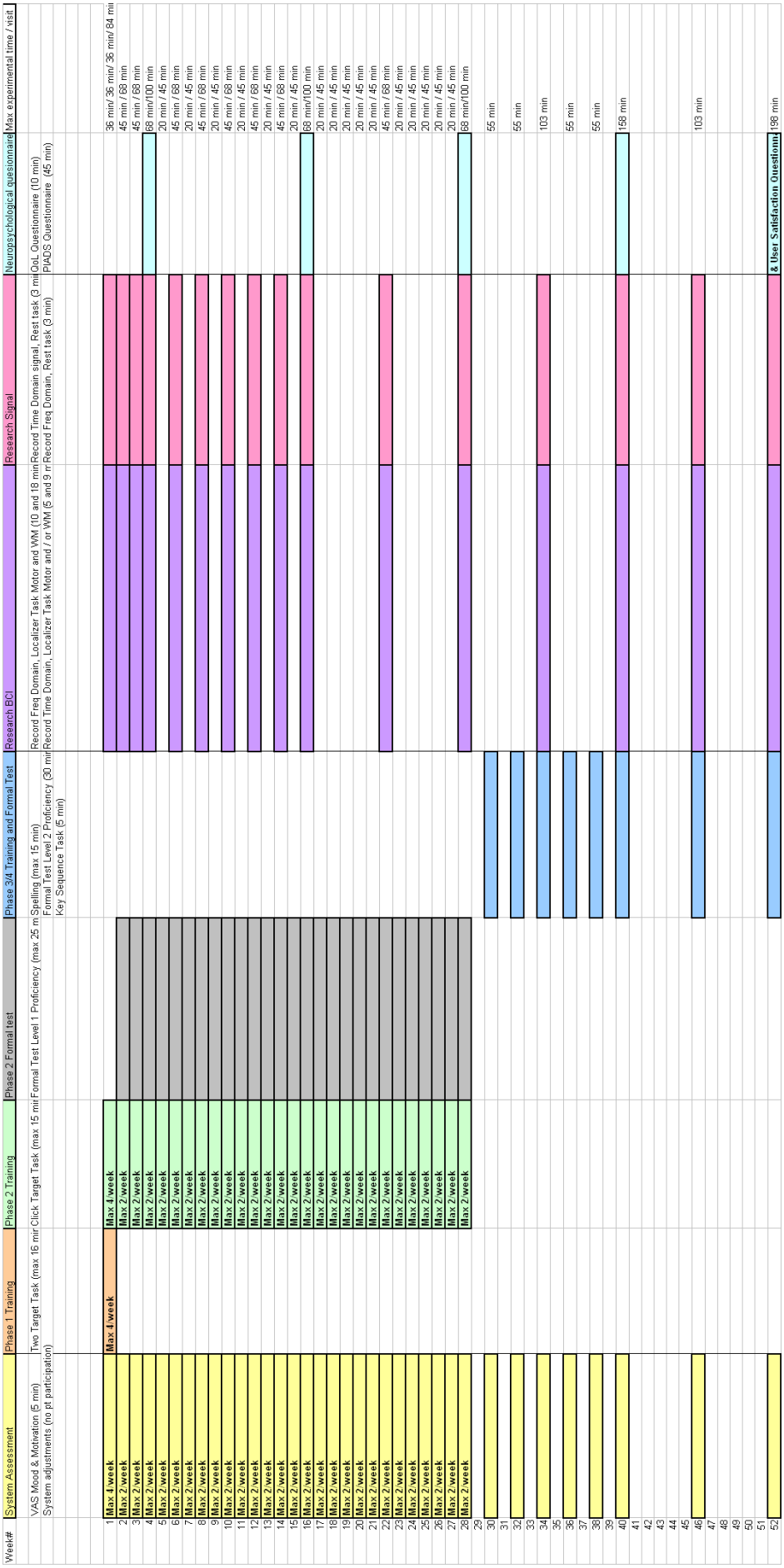
A. Example of a quick scenario, in which the patient reaches first level of proficiency within 4 weeks after implantation. In this case, the frequency of visits will decrease after 4 weeks, and Phase 3 and Phase 4 training will commence. Note that green and yellow columns are related to BCI performance by the patient, whereas purple, pink and blue are related to data collection for research purposes only. The planning of this research data collection is fixed and independent of the BCI training progress.

B. Example of a slow scenario, in which the patient reaches first level of proficiency just before the critical decision moment at 28 weeks after implantation, after which the frequency of visits will decrease and Phase 3 and Phase 4 training will commence. Note that green and yellow columns are related to BCI performance by the patient, whereas purple, pink and blue are related to data collection for research purposes only. The planning of this research data collection is fixed and independent of the BCI training progress (unless the patient is excluded from further study because of not reaching level 1 proficiency within 28 weeks after implantation, in that case, also data collection for research is terminated at that point).

A


Week#
System Assessment
Phase 1 Training
Phase 2 Training
Phase 2 Formal test
Phase 3/4 Training and Formal Test
Research BCI
Research Signal
Neuropsychological quesionnaire
Max experimental time / visit
VAS Mood & Motivation (5 min)
System adjustments (no pt participation)
Two Target Task (max 16 mi
Click Target Task (max 15 mi
Formal Test Level 1 Proficiency (max 25 mi
Spelling (max 15 min)
Formal Test Level 2 Proficiency (30 min)
Key Sequence Task (5 min)
Record Freq Domain, Localizer Task Motor and WM (10 and 18 mi
Record Time Domain, Localizer Task Motor and / or WM (5 and 9 r
Record Time Domain signal, Rest task (3 mir
Record Freq Domain, Rest task (3 min)
QoL Questionnaire (10 min)
PIADS Questionnaire (45 min)
Max 4/week
Max 4 / week
Max 2/week
36 min / 36 min / 36 min / 84 m
45 min / 68 min
45 min / 68 min
68 min/ 100 min
103 min
158 min
& User Satisfaction Questionn
198 min

B


Week#
System Assessment
Phase 1 Training
Phase 2 Training
Phase 2 Formal test
Phase 3/4 Training and Formal Test
Research BCI
Research Signal
Neuropsychological quesionnaire
Max experimental time / visit
VAS Mood & Motivation (5 min)
Two Target Task (max 16 min
Click Target Task (max 15 min
Formal Test Level 1 Proficiency (max 25 m
Spelling (max 15 min)
Record Freq Domain, Localizer Task Motor and WM (10 and 18 min
Record Time Domain signal, Rest task (3 min
QoL Questionnaire (10 min)
System adjustments (no pt participation)
Formal Test Level 2 Proficiency (30 min
Record Time Domain, Localizer Task Motor and / or WM (5 and 9 m
Record Freq Domain, Rest task (3 min)
PIADS Questionnaire (45 min)
Key Sequence Task (5 min)
Max 4 week
Max 2 week
36 min/ 36 min/ 36 min/ 84 min
45 min / 68 min
68 min/100 min
20 min / 45 min
55 min
103 min
158 min
198 min
& User Satisfaction Questionn

Home Use and Data Collection Standard Operating Procedure

Executive summary

This Standard Operating Procedure (SOP) has been designed to support the research team of the UNP project in the safe and correct execution of the study protocol, part 'Home Use and Data Collection'. It describes the procedure during the research visits of members of the research team at the patient's home. If something is unclear, contact the study coordinator.

1. Consult patient and caretaker on functioning of the BCI system
2. Copy updates from the caretaker log
3. Press Patient Button on Streaming Unit to switch off
4. Take off antenna
5. Use the N'Vision Clinician Programmer to check battery level from Start Session screen (Fig 1): Log battery status and voltage

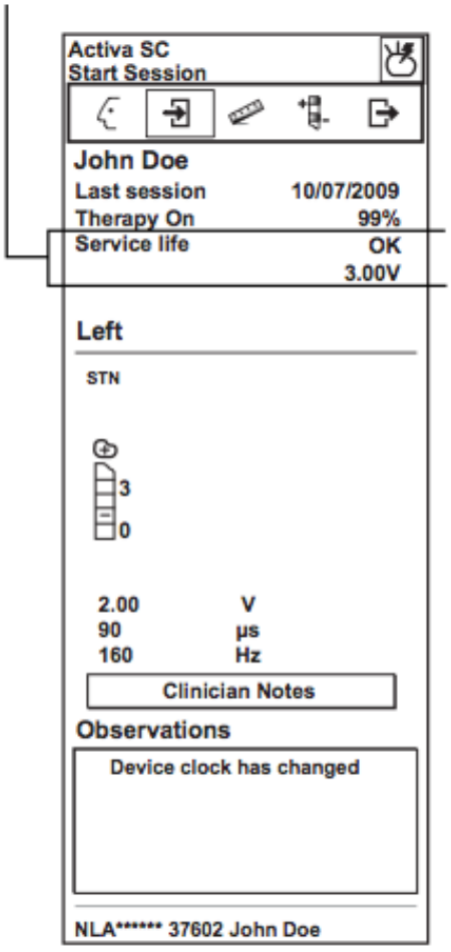


Figure 1

6. Use the N'Vision Clinician Programmer to check impedance as follows:
   6.1. Access the Measurement menu and select Electrode Impedance.

6.2. Select the Left (hemisphere) tab or the Right (hemisphere) tab (Fig 2).
6.3. Select the Settings button (Fig 3).

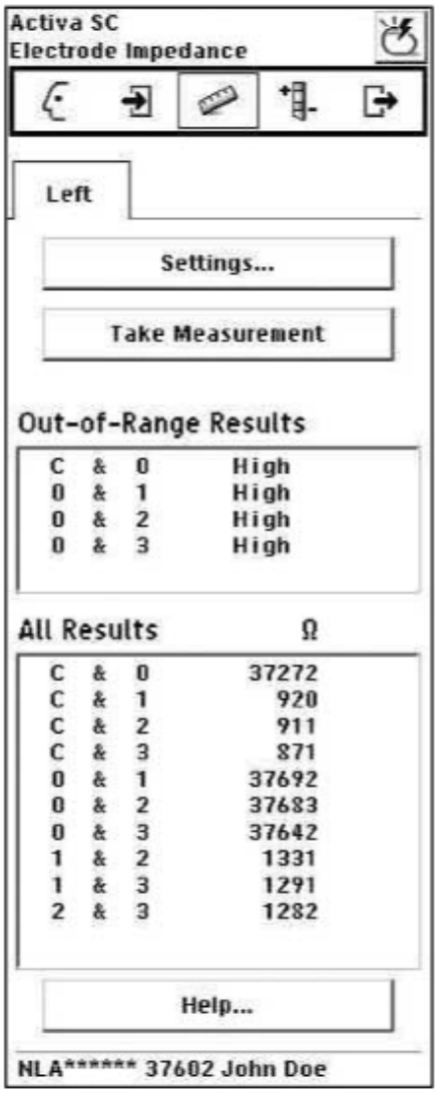


Figure 2

6.4. Select 0.25V amplitude value from the drop-down list.
6.5. Select Bipolar as electrode configuration option.
6.6. Select all electrodes to test.
6.7. Select the OK button.
6.8. Position the programming head over the neurostimulator, then select the Take Measurement button.
6.9. Select the OK button and maintain the position of the programming head over the neurostimulator for the duration of the test. To stop the electrode impedance test before all electrodes are tested, select the Cancel button

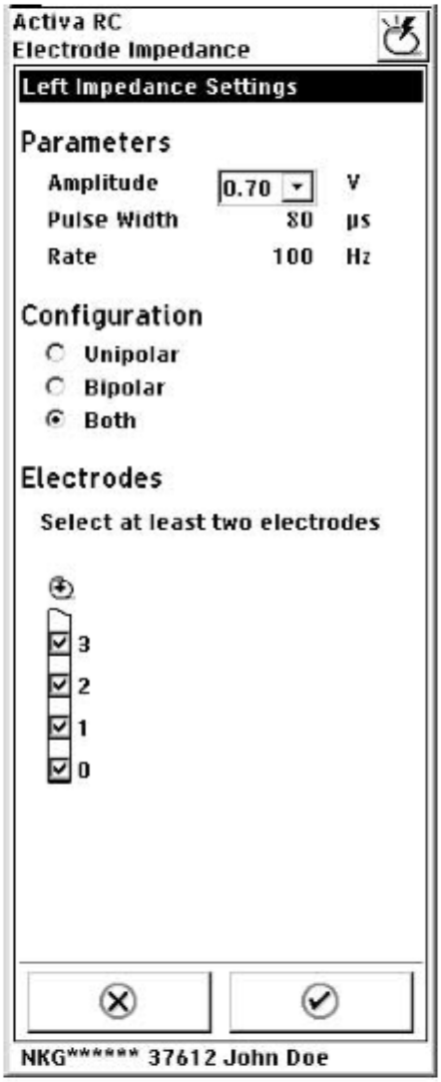


Figure 3

6.10. Review and log the electrode impedance test results. Note: If any measurements are above the range for the selected amplitude setting, a prompt appears to repeat the high measurement at the next higher amplitude setting.

6.11. Select End Session and check that stimulation parameters are at lowest amplitude (i.e. 0V), lowest frequency (i.e. 2Hz) and lowest pulse width (i.e. 60us), cycling is ON with ON/OFF periods 0.1s/24h

6.12. Select Exit and check whether a warning appears that stimulation is off. **Stimulation should be off!**

7. Conduct VAS Mood and Motivation
8. Connect research laptop to Brain Interpreter via USB Ethernet Adapter using a cross link UTP cable.
   8.1. Set static IP address 192.168.0.1
   8.2. Log in the Remote Desktop
   8.3. Connect mobile harddisk and copy new data files from Brain Interpreter
   8.4. Set new parameters, including new pipeline files, if necessary.

8.5. Close Remote Desktop Connection

9. Set Activa PC + S sensing to time domain:
    9.1. Connect the SPTM to the Sense Programmmer and the antenna.
    9.2. Place the antenna over the Activa PC+S
    9.3. Start Sense Programming software.
    9.4. Log current parameters.
    9.5. Choose relevant channels. Set sensing type to Time (200 Hz).
    9.6. Set sensing enabled.
    9.7. End session.
10. Connect streaming unit to the research computer via Serial to USB adapter. Perform research tasks with Time Domain.
11. Set Activa PC + S sensing to frequency domain:
    11.1. Connect the SPTM to the Sense Programmmer and the antenna.
    11.2. Place the antenna over the Activa PC+S
    11.3. Start Sense Programming software.
    11.4. Set parameters to new values if necessary.
    11.5. Choose relevant channels. Set sensing type to Power (5 Hz).
    11.6. Log current parameters.
    11.7. Set sensing enabled.
    11.8. End session.
12. Connect streaming unit to the research computer via Serial to USB adapter. Perform research tasks with Frequency Domain.
13. If necessary do training and or proficiency test.
14. The order of tasks may change, but always end with a task with frequency domain, to ensure that time domain is not on, when the research team leaves the patient’s home.
15. Reconnect the streaming unit to the Brain Interpreter.

N'Vision: Battery Level	□		
N'Vision: Impedance measurement	□	0-1 0-2 0-3 1-2 1-3 2-3	8-9 8-10 8-11 9-10 9-11 10-11
N'Vision: Warning message that Stimulation is OFF?	□		
Logbook caretaker	□		
VAS Mood & Motivation	□		
Activa PC+S Sensing parameters	□		
Tasks time domain			
Motor rest	□		
Motor localizer	□		
WM rest	□		
WM localizer	□		
Tasks frequency domain			
Motor rest	□		
Motor localizer	□		
WM rest	□		
WM localizer	□		
Other if applicable			
Proficiency level …	□		
New Activa PC+S Sensing parameters	□		
	□		
	□		

Checklist volledig | Datum:……..|Tijd:……|Paraaf:……

15.5 Selection of target regions for electrode placement

Extensive prior research has been conducted at the UMC Utrecht on the optimal locations on the cortical surface for BCI. We aim to implant electrodes on 2 regions, each representing a different function, to maximize chances of obtaining good control for BCI. Targeting 2 functions increases chances of finding a good focus, and increases chances of good mental control (some may prefer imagery/attempt, others counting backwards).The two target regions are based on Cognitive Control and Motor Imagery/Attempt. Cognitive control has yielded by far the best results in our series of tests in epilepsy patients with implanted electrode grids, in that all patients rapidly gained control over a cursor based on changes in gamma power on either dorsolateral prefrontal cortex or superior parietal cortex. Good performance is defined by both 'hit rate' (correct decoding of an intended cursor movement) and 'false positive rate' (decoded intentions where none was generated). The latter is typically caused by other functions activating the same brain region, for instance listening to speech activating language production regions. Hence choice of target region must be based on both measures. The DLPFC has proven to be highly selective in our previous paper on cognitive control (Vansteensel et al., 2010). Further investigation of 24 hours of non-task measurement has shown that false positive rates can be brought down to a very low level for DLPFC (Torres Valderrama et al., 2012). We have recently proven that electrode pairs can generate superior features for BCI control, as compared to common average correction (which requires a larger electrode grid), further supporting feasibility of obtained good BCI signal from the 4-electrode strips available for the present study. This document provides details on those (unpublished) findings.

For the motor imagery function we have obtained excellent results for one epilepsy patient, with electrodes placed on premotor cortex (i.e. not primary motor cortex) (Hermes et al., 2011b). In that study we show that healthy volunteers fail to activate primary motor cortex with motor imagery. For paralyzed people it is not clear whether motor imagery works for primary motor cortex, and for this reason we target the premotor region. However, there is some evidence that paralyzed people can attempt to make movements, and that this yields better results for motor cortex (Hotz-Boendermakers et al., 2008). Evidence is scarce for this but we believe we should keep an open mind in this regard. This is in fact feasible without sacrificing chances of obtaining good signal because premotor and motor cortex are positioned quite close to each other. Hence we will be able to place strips covering both, allowing for testing both imagined and attempted movement after electrode placement, before selecting specific electrode pairs.

Figure 15.5.1 shows the regions of interest, which were based on group-averaged results from several experiments with healthy volunteers (not part of the BCI research). The yellow rectangles show the regions where we find good activation in healthy volunteers, and where we have found good electrodes for BCI in the epilepsy grid patients.

Validation of fMRI-based electrode position selection

In the 3T MRI scanner epilepsy patients performed a mental calculation task before electrode implant surgery. The fMRI data were analyzed with SPM8, with standard preprocessing and GLM analysis. Data remained in native space to allow for co-registration with the post-implant CT scan which reveals the exact electrode locations. To get the fMRI results in the same space as the electrode coordinates obtained from the CT scan we use a custom made software package published in 2010 (Hermes et al., 2010). The principal investigator evaluated the fMRI results without knowledge of the electrode positions and performed two procedures.

First he identified the coordinates of the strongest activating voxels within a predefined Region of Interest (see Figure 15.5.1), in existing data. The predefined Region was based on brain activity maps obtained in a large sample of healthy volunteers with a verbal cognitive control task and on results obtained with the first three participants published in 2010 (Vansteensel et al., 2010). The hypothesis was that the fMRI peak voxels represented neural tissue that generates good ECoG signal for BCI. These coordinates were sent to another member of the research team who then identified the electrodes nearest the fMRI foci and computed the r-square value of performance on a mental calculation task for that particular electrode. Hypothesis testing involved computing the correlation between fMRI t-value and ECoG r-square value. fMRI foci were good indicators but have a margin of error in the order of 10 mm. This is in agreement with our studies on correlations between ECoG and fMRI activation maps (Hermes et al., 2011a, Hermes et al., submitted).

The second procedure was applied to new participants. After fMRI scanning, and in anticipation of the present proposed implant of 4-electrode strips, the principal investigator now defined two lines of about 4 cm on the cortical surface, again with Mricron, capturing the strongest activation foci within the Region of Interest. Again, the coordinates were sent to another researcher who identified the nearest grid electrodes to each of point along the indicated lines. In two patients, electrode pairs were selected based on the fMRI-based lines and BCI was attempted with bipolar signal. After the experiments the data were interrogated for any other bipolar or unipolar signal that would have been better than the selected electrode pair. In both cases, excellent electrode pairs were found, with high BCI performance (Figures 15.5.2 and 15.5.3). In both patients the BCI control task was performed with bipolar signals in realtime. The first patient (Figure 15.5.2) was tested three times (each task lasts approximately 5 minutes), and scores 70%, 73 % and 94 % respectively (chance is 50%). The second patient (Figure 15.5.3) performed the task once, and immediately scored 92 % on the task. Posthoc comparison with uni-and bipolar signals revealed that the pair chosen yielded the highest r-square during the task of all tested pairs (within indicated 4 cm lines) and for all unipolar signals for those electrodes.

For the motor region we have not been able to test bipolar electrode pairs for BCI. We did, however, obtain excellent results for a unipolar electrode on premotor cortex in a single patient (Figure 15.5.4). This patient performed the control task six times with imagined

movement of the left hand, and achieved an average of 91% correct (chance is 50%). Note that her electrode placement was on the right hemisphere. FMRI predicted this spot quite accurately (Figure 15.5.4).

In summary, fMRI as obtained with the clinical scan techniques (3D-PRESTO) yields accurate target coordinates for electrode implant. However, a margin is observed of about 10 mm. To maximize chances of covering the best performing foci we therefore implant 2 strips side-by-side on the region indicated by fMRI, for each of the two target functions (cognitive control and hand motor imagery/attempt).

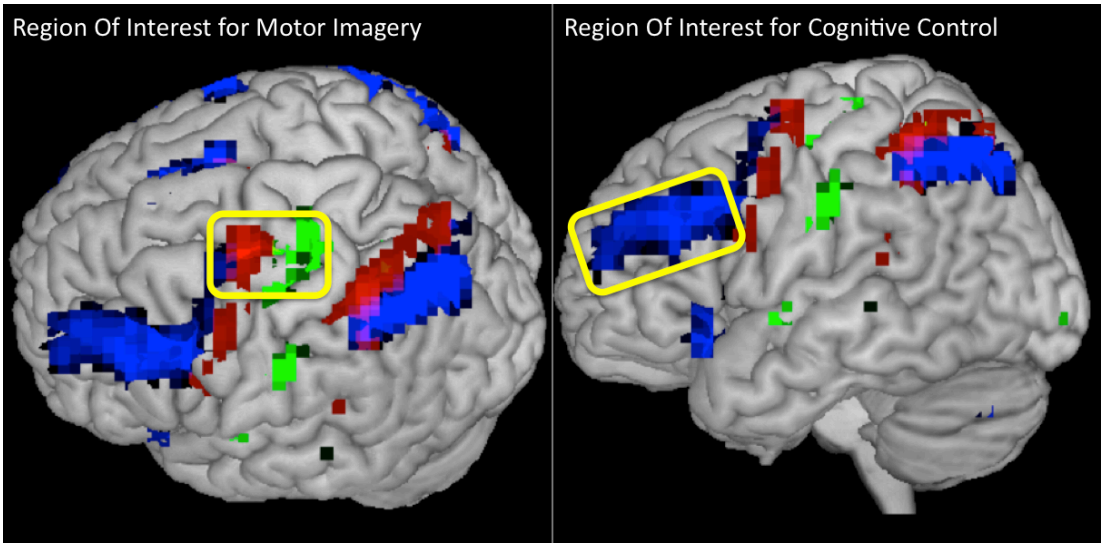


Figure 15.5.1: Regions of Interest for electrode placement based on imaging experiments in groups of healthy subjects at the UMC Utrecht: In blue activity for Cognitive Control, in red activity for Imagined hand movements and in green actual hand movement. For individual patients the peak values voxels within a region (yellow rectangles) are used for electrode placement. See text for further explanation.

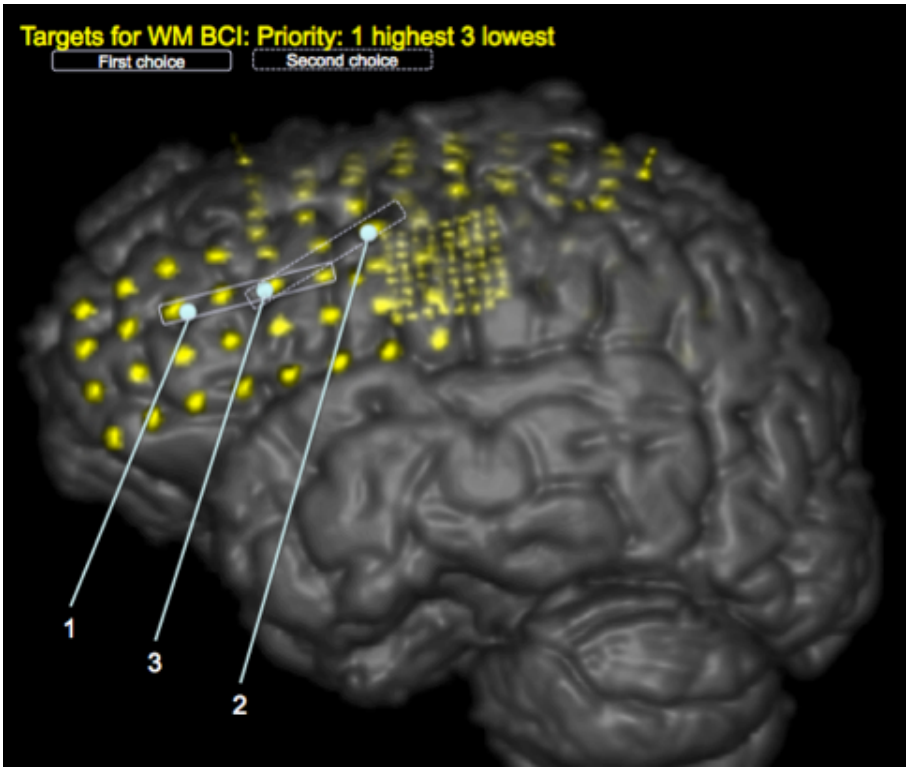


Figure 15.5.2: Patient 1: the strip positions were indicated solely on the basis of fMRI activity maps (not shown). The coordinates were then projected onto the electrode rendering shown here, resulting in identification of candidate electrode sets for BCI control.

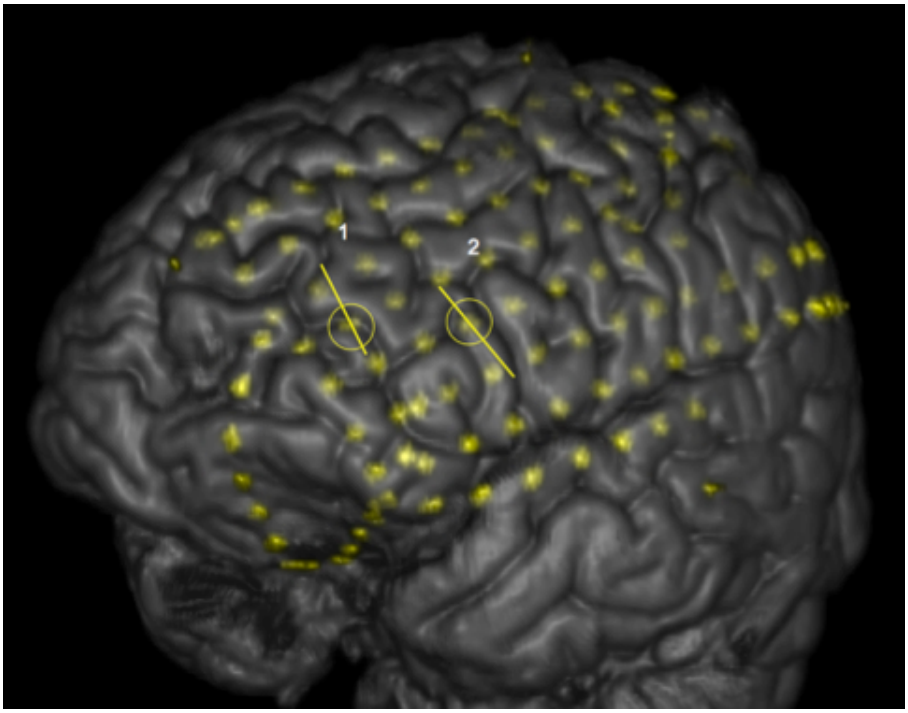


Figure 15.5.3: Same as figure 15.5.2, for a different patient

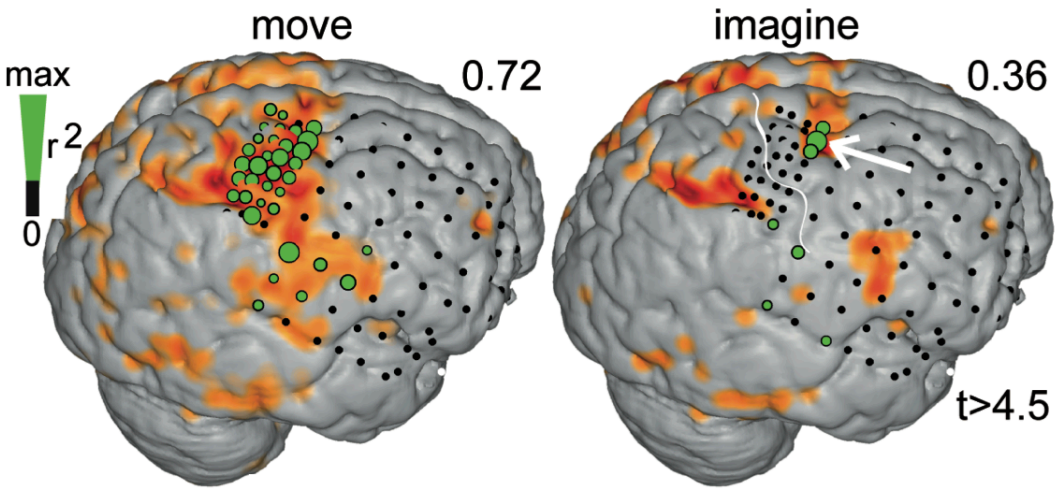


Figure 15.5.4: electrode used for BCI control based on Motor Imagery (imagined hand movement) in one grid patient, indicated by white arrow. Size of green dots indicates strength of correlation of gamma power changes with localiser task execution (left: a motor task, right: a movement imagery task). The primary motor cortex does not activate during imagery but the premotor region does (white arrow). In orange the fMRI activity is displayed. Note the high concordance between fMRI activity and the best performing electrode (white arrow).

15.6 Surgery-Standard Operating Procedure and Checklists

Surgery Standard Operating Procedure 1

Executive summary

This Standard Operating Procedure (SOP) has been designed to support the dedicated and trained subgroup of the research team of the UNP project in the safe and correct execution of the study protocol, part 'Surgery-Procedure 1'. The SOP has to be completed entirely at all times. If something is unclear, contact the principal investigator.

Full description of procedures

TIMELINE PROCEDURE 1

Team Briefing

In a team briefing, the research team, neurosurgical and anesthesiology team will receive a detailed explanation about the procedure by the study coordinator.

Surgical procedure 1

ICU — The patient is subject to normal peri-operative procedures used at the department of neurosurgery at the University Medical Center Utrecht. The resident, nurse and neurosurgeon complete the

- *Checklist SURPASS*

Holding area — According to normal pre-operative procedures, an intra-venous canula is placed and connected to a Saline drip to prevent the canula from clotting. If the patient is on a ventilator he is transferred to the recovery area of the OR center. From there the patient is transferred to the operating theatre. The research team completes the

- *Checklist UNP equipment 1*

OR — After placing a maximum of four subdural strips, the leads are tunneled subgaleally to the area where the connectors will be placed (preferably temporoparietal at the hemisphere of implantation), and marked by a wire-specific Mersilene ligature. Lead identification info is written down by the study coordinator. From there, permanent extensions are tunneled to the thorax. Temporary percutaneous extensions are tunneled to the abdomen, where they are externalized and marked by Mersilene ligatures. Lead identification will be written down by the study coordinator. After fixating the leads, an expert from the ECoG

	Team will evaluate the signal quality assuring that the electrodes have good contact with the brain. The research team completes the - *Checklist procedures 1*
Recovery	The patient is subject to normal post-operative care before he will be transferred back to the ICU. The study coordinator collects all checklists, and calls a team debriefing when complications have occurred, or any team member wishes to debrief the procedure. The study coordinator completes the - *Checklist study coordinator 1*

<u>End of the Surgery Procedure</u>

People involved
Research team / principle investigator
Research team / study coordinator
Neurosurgery team
Anesthesiology team

Surgery Standard Operating Procedure 1 (Checklists)

Checklist Study coordinator 1

		Before procedure
Team Briefing	□	
fMRI data available for neuronavigation?	□	
Fiducials still in place?	□	
		ICU
Neurosurgery team: SURPASS Checklist	□	
		OR
Research team: Checklist UNP Equipment 1	□	
Research team: Checklist Procedures 1	□	

Checklist volledig | Datum:……..|Tijd:……|Paraaf:……

Surgery Standard Operating Procedure 1 (Checklists)

Checklist UNP Equipment 1

4x subdural leads + manual	□	Batchnumber:……
4x Permanent extension leads + manual		
4x Temporary extension leads + manual	□	
2x Trialing cable + manual	□	
2x Touchproof adapter + manual	□	
Micromed System	□	

Checklist volledig | Datum:……..|Tijd:……|Paraaf:……

Surgery Standard Operating Procedure 1 (Checklists)

Checklist Procedures 1

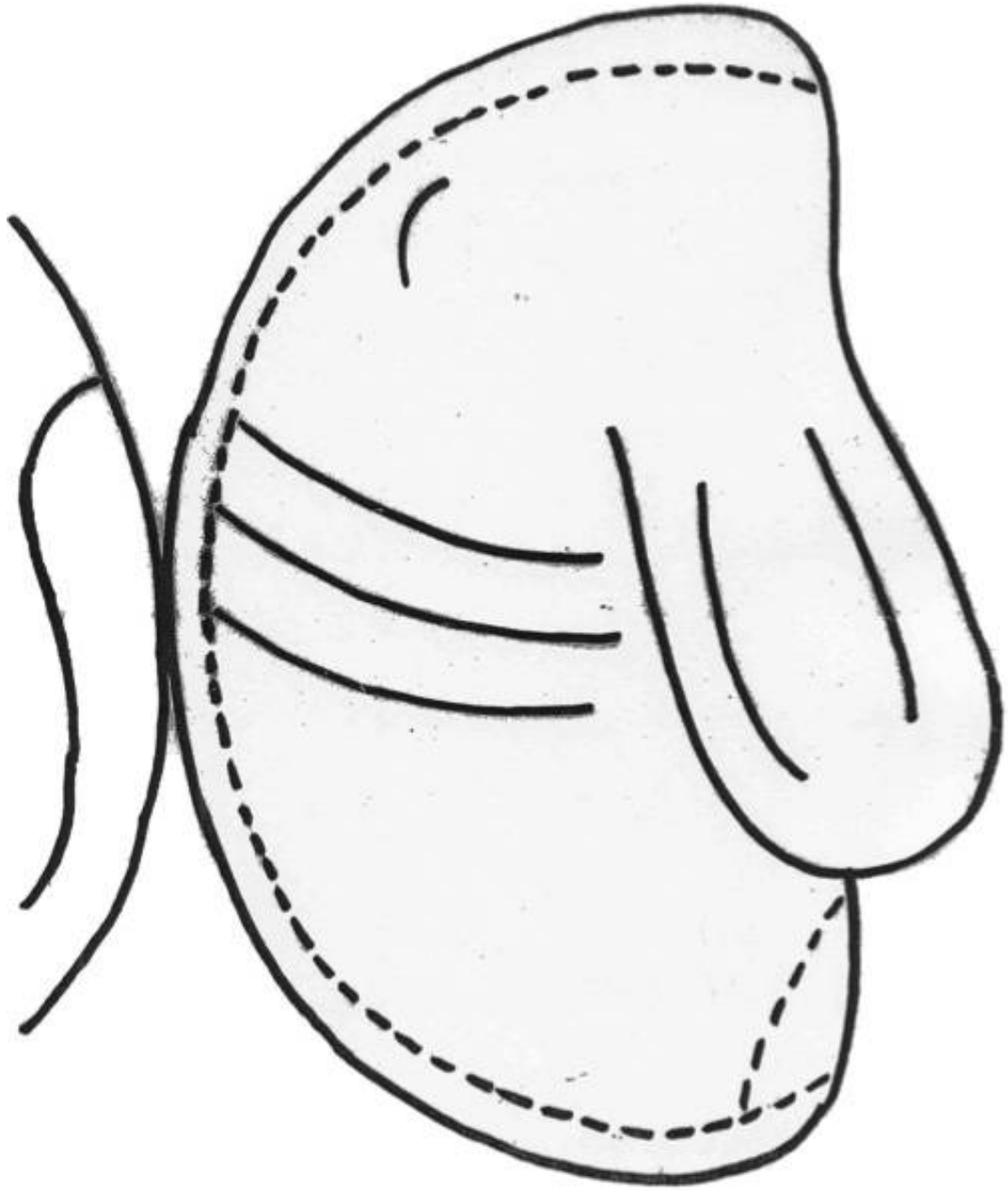
Motor Procedure

2 subdural electrode strips over premotor-motor areas?	□	
Contacts not on large blood vessels?	□	
Leads labeled?	□	Label Strip 1: Location Strip 1: Label Strip 2: Location Strip 2:
Check signal quality after closing dura	□	
Check signal quality after tunneling	□	

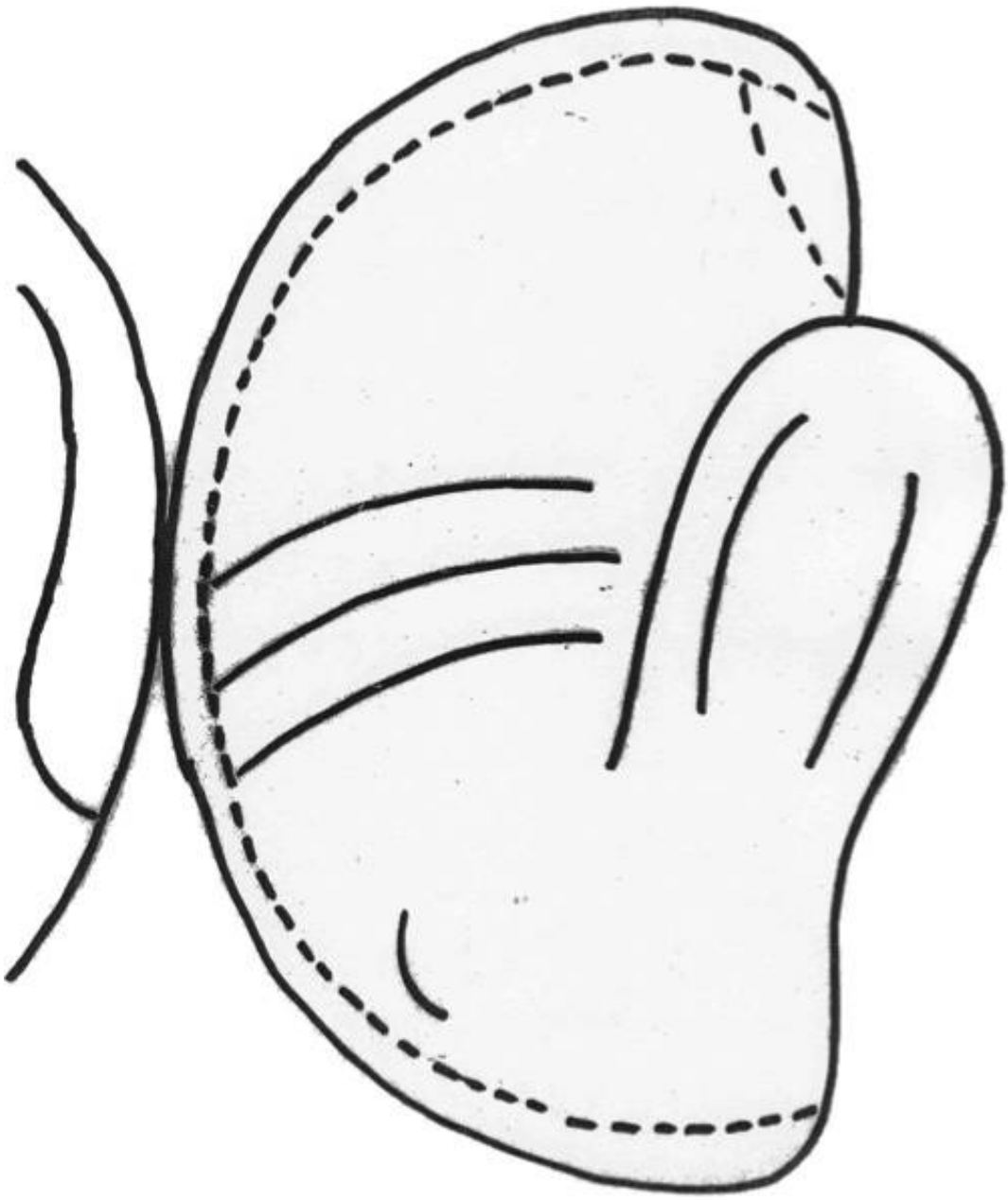
WM Procedure

2 subdural electrode strips over working memory area of DLPFC?	□	
Contacts not on large blood vessels?	□	
Leads labeled?	□	Label Strip 3: Location Strip 3: Label Strip 4: Location Strip 4:
Check signal quality after closing dura	□	
Check signal quality after tunneling	□	

Indicate Locations Strips Here – Left Hemisphere



Indicate Locations Strips Here – Right Hemisphere



Checklist volledig | Datum:……..|Tijd:……|Paraaf:……

Surgery Standard Operating Procedure 2

Executive summary

This Standard Operating Procedure (SOP) has been designed to support the dedicated and trained subgroup of the research team of the UNP project in the safe and correct execution of the study protocol, part 'Surgery-Procedure 2'. The SOP has to be completed entirely at all times. If something is unclear, contact the principal investigator.

Full description of procedures

TIMELINE PROCEDURE 2

Team Briefing

In a team briefing, the research team, neurosurgical and anesthesiology will receive a detailed explanation about the procedure by the study coordinator.
The study coordinator programs a warning message in the Activa PC + S not to activate stimulation, enables one group and sets safe stimulation parameters (at lowest amplitude (i.e. 0V), lowest frequency (i.e. 2Hz) and lowest pulse width (i.e. 60us), cycling is ON with ON/OFF periods 0.1s/24h). He will also ensure that information on the Activa PC + S (serial number, MRI incompatibility), participation in UNP study is added to the patient dossier.

Surgical procedure 2

ICU	The patient is subject to normal peri-operative procedures use at the department of neurosurgery at the University Medical Center Utrecht. The resident, nurse and neurosurgeon complete the - *Checklist SURPASS*
Holding area	According to normal pre-operative procedures, an intra-venous canula is placed and connected to a Saline drip to prevent the canula from clotting. If the patient is on a ventilator he is transferred to the recovery area of the OR center. From there the patient is transferred to the operating theatre. The research team completes the - *Checklist UNP equipment 2*
OR	Surgery will be performed according to normal clinical procedures. After prepping the skin at the connector site and thoracic area with chloorhexidine, the connector site is opened and the extension cables are disconnected. The extension cables are removed at the site of externalization.

	A subcutaneous pouch is made and the device is connected to two cables and placed in the pouch. The tips of the other cables are capped. After the Activa PC+S is in place and the electrodes are connected, proper functioning of the Activa P+S is ensured. The wound is closed in two layers. The incision is closed in two layers. The wound is covered by a patch. The research team completes the - *Checklist procedures 2*
Recovery	The patient is subject to normal post-operative care before he will be transferred back to the ICU.

The study coordinator collects all checklists, and calls a team debriefing when complications have occurred, or any team member wishes to debrief the procedure. The study coordinator completes the

- *Checklist study coordinator 2*

<u>End of the Surgery Procedure</u>

People involved

Research team / principle investigator
Research team / study coordinator
Neurosurgery team
Anesthesiology team

Checklist Study coordinator 2

		Before procedure
Team Briefing	□	
To-be-connected electrodes clear?	□	
Identification of target electrodes clear?	□	
Activa PC + S: Warning message set?	□	
Activa PC + S: Only 1 group enabled?	□	
Activa PC + S: Stimulation parameters safe?	□	
Activa PC + S: Serial number in patient file?	□	
Activa PC + S: MRI incompatibility in patient file?	□	
		ICU
Neurosurgery team: SURPASS Checklist	□	
		OR
Research team: Checklist UNP Equipment 1	□	
Research team: Checklist Procedures 1	□	

Checklist volledig | Datum:……..|Tijd:……|Paraaf:……

Checklist UNP Equipment 2

2x Caps to cap unused leads	□	
Activa PC+S	□	Serial number =……
Instruction of implantation Activa PC+S	□	
Dedicated screwdriver with torque restriction	□	
Sense Programmer with charged battery + SPTM	□	

Checklist volledig | Datum:……..|Tijd:……|Paraaf:……

Checklist Procedures 2

Two unused leads capped?	□	Label: Label:
Two target leads connected to Activa PC+S?	□	Label: Label:
Screws tightened with dedicated screwdriver until first click?	□/□	
Functioning of Activa PC+S checked using SPTM and Sense Programmer?	□	

Checklist volledig | Datum:……..|Tijd:……|Paraaf:……

15.7 SURPASS Checklist

PRE-OPERATIEF op de afdeling
<u>Aanvulling verpleegkundige anamnese</u>
In te vullen door verpleegkundige

Patiëntsticker

Veranderingen in de gezondheid?

		Nee	Ja
1.	Bent u tussen uw bezoek aan de POS polikliniek en vandaag bij uw huisarts geweest?	O	O*
2.	Bent u tussen uw bezoek aan de POS polikliniek en vandaag ziek geweest?	O	O*
3.	Is er tussen uw bezoek aan de POS polikliniek en vandaag iets veranderd in het gebruik van uw medicijnen?	O	O*
4.	Bent u tussen uw bezoek aan de POS polikliniek en vandaag opgenomen geweest in een ziekenhuis?	O	O*

Bij één of meer antwoorden '**ja',** indien relevant**: **overleg met de zaalarts én noteren in EPD** (= brondocument).
Indien de zaalarts niet kan beoordelen of het antwoord relevant is voor de ingreep en/of anesthesie dan kan hij/zij overleggen met de anesthesioloog die de patiënt anesthesie zal geven.
** het stoppen van anticoagulantia als voorbereiding op operatie geeft een ja op vraag 3, maar vereist geen overleg met de zaalarts.

Datum: ……Verpleegkundige:……..

PRE-OPERATIEF op de afdeling
<u>Voor transport naar holding</u>
In te vullen door zaalarts
maximaal 24 uur voor de operatie

Patiëntsticker

		Niet van toepassing	Ja
1.	Patiënt is gezien, en indien nodig onderzocht, door zaalarts		O
2.	Informed consent (voor operatie) is in status geregistreerd en met patiënt besproken		O
3.	Medische gegevens (inclusief brieven en eerdere operatieverslagen) zijn gezien door zaalarts		O
4.	Relevante imaging is beoordeeld en beschikbaar	O	O
5.	Relevante consulten door andere specialismen zijn verricht	O	O
6.	Preoperatieve adviezen van anesthesioloog / andere specialismen zijn opgevolgd	O	O
7.	Relevante laboratoriumcontroles (kruisbloed) zijn verricht en bloed is gereserveerd	O	O
8.	Medicatieafspraken zijn gemaakt en genoteerd		O
9.	Antistolling* Laatste dosis laag moleculaire heparines (LMWH, bijvoorbeeld dalteparine of fraxiparine) is:		
	a) Niet toegediend ivm nuchtere opname	O	O
	b) Therapeutische dosis ≥ 24 uur geleden toegediend	O	O
	c) Profylactische dosis ≥ 10 uur geleden toegediend	O	O
10.	Antistolling*		
	a) Orale antistolling (acenocoumarol/fenprocoumon) gestopt/doorgebruikt volgens afspraken op POS?	Niet van toepassing / Ja / Nee	
	b) Thrombocytenaggregatieremmers gestopt/doorgebruikt volgens afspraken op POS?	Niet van toepassing / Ja / Nee	

* Uitgezonderd cardio- en vaatchirurgie

Datum: …….. Naam en paraaf zaalarts:……..

PRE-OPERATIEF op de afdeling
<u>voor transport naar holding</u>
In te vullen door verpleegkundige

Patiëntsticker

		Niet van toepassing	Ja
1.	Patiënt is conform (of specifieke) afspraak voorbereid op ingreep en op anesthesie (inclusief: nuchterbeleid gevolgd?)		O
2.	Patiënt is volgens protocol gewassen met hibiscrub (inclusief haren) en voorbereid met bactroban	O	O
3.	Voorgeschreven (ziekenhuis) medicatielijst is in verpleegkundige status aanwezig		O
4.	Decubitusscreening en -preventie is volgens protocol uitgevoerd en vastgelegd	O	O
5.	Delierscreening en –preventie zijn volgens protocol uitgevoerd en vastgelegd	O	O
6.	Valscreening en –preventie zijn volgens protocol uitgevoerd en vastgelegd	O	O
7.	Voedingsstatus gescreend en overlegd met arts	O	O
8.	Naambandje om arm		O
9.	Gebitsprotheses, piercings etc. zijn verwijderd	O	O
10.	Statussen zijn bij patiënt aanwezig (klinisch, poliklinisch, anesthesie, verpleegkundig) en beeldvormende diagnostiek / neuronavigatie		O
11.	SURPASS checklist zaalarts is ingevuld en getekend		O

Datum: ……Verpleegkundige:……..

PRE-OPERATIEF op de afdeling
<u>voor transport naar holding / of</u>
<u>op holding</u>
In te vullen door operateur maximaal 24 uur voor de operatie

Patiëntsticker

		Niet van toepassing	Ja
1.	Patiënt is gezien door operateur		O
2.	Operatiezijde is, volgens protocol, gemarkeerd	O	O
3.	Informed consent is verkregen en in status geregistreerd		O
4.	Medische gegevens die noodzakelijk zijn om de operatie uit te voeren, en informatie op OK-programma zijn correct (details ingreep, positie, operatietechniek etc)		O

Datum: …….. Naam en paraaf operateur……..

Voor ontslag uit ziekenhuis

In te vullen door zaalarts (na overleg met de operateur/ hoofdbehandelaar)

Patiëntsticker

		Niet van toepassing	Ja
1.	Overleg operateur/hoofdbehandelaar met zaalarts heeft plaatsgevonden		O
2.	Patiënt is geïnformeerd over aard ingreep en verloop.		O
3.	PA uitslag is besproken O PA volgt	O	O
4.	Patiënt heeft instructies t.a.v. wondverzorging gekregen	O	O
5.	Patiënt heeft instructies t.a.v. dieet gekregen	O	O
6.	Patiënt heeft instructies t.a.v. medische hulpmiddelen (bv drain, catheter, kraag) gekregen	O	O
7.	Patiënt heeft instructies t.a.v. antistolling gekregen	O	O
8.	Patiënt heeft instructies t.a.v. lichamelijke activiteiten, inspanning en werkhervatting gekregen		O
9.	Medicatielijst is gecontroleerd		O
10.	Opdracht voor poliklinische afspraak chirurgie/ andere specialismen is gegeven		O
11.	(Voorlopige) ontslagbrief huisarts is geschreven (en telefonisch doorgegeven in geval van complicaties, ontslag met open wond, drains, etc.)		O
12.	Ontslagbrief (bij overplaatsing naar ander ziekenhuis, revalidatiecentrum, etc.) is geschreven	O	O

Datum: …….. Naam en paraaf zaalarts:……...

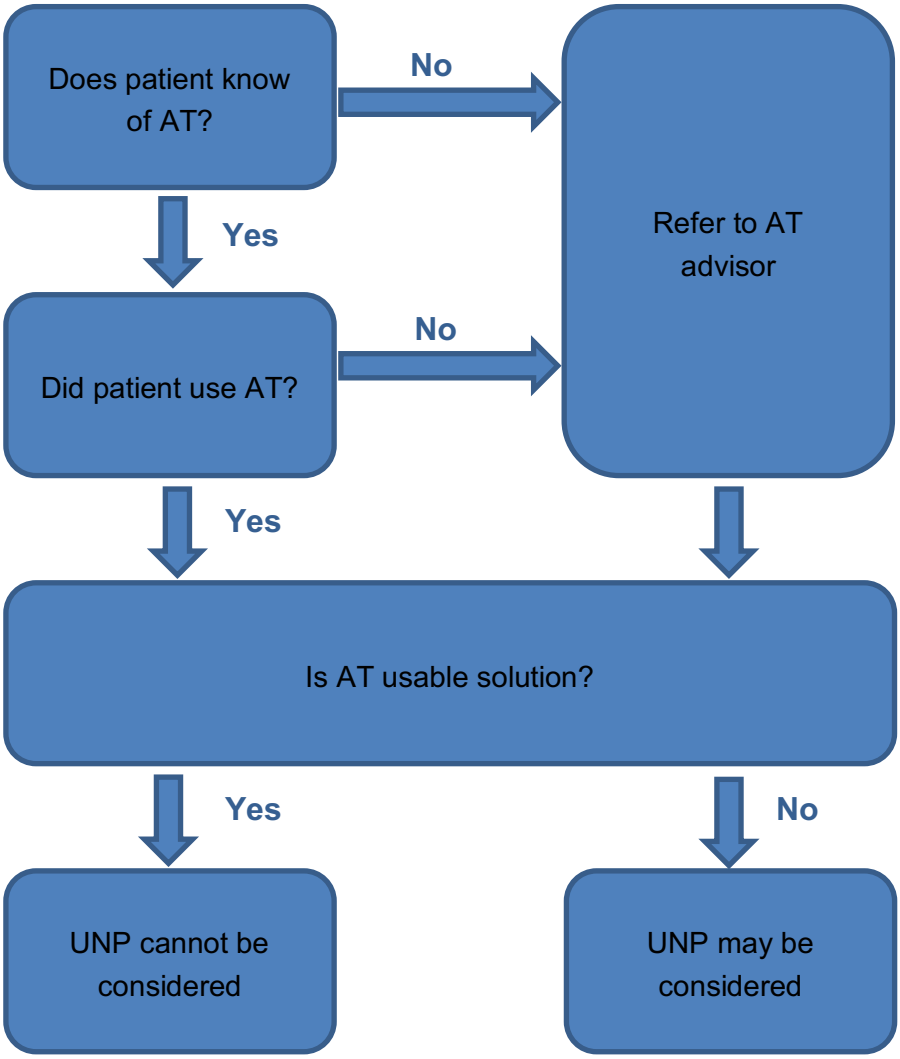
Voor ontslag uit ziekenhuis
In te vullen door verpleegkundige

Patiëntsticker

		Niet van toepassing	Ja
1.	Checklist voor ontslag is door zaalarts ingevuld		O
2.	Instructies t.a.v. leefregels thuis zijn aan patiënt uitgelegd		O
3.	Instructies t.a.v. wondverzorging zijn aan patiënt uitgelegd		O
4.	Instructies t.a.v. dieet zijn aan patiënt uitgelegd	O	O
5.	Instructies t.a.v. drains, voedingsfistel zijn aan patiënt uitgelegd	O	O
6.	Instructies t.a.v. optreden complicaties thuis zijn aan patiënt uitgelegd		O
7.	Instructies t.a.v. medicatie thuis zijn aan patiënt uitgelegd	O	O
8.	Heeft patiënt item 2 tot en met 7 begrepen?		O
9.	Door arts ondertekend recept is aanwezig	O	O
10.	Poliklinische afspraak chirurgie / andere specialismen is / zijn gemaakt		O
11.	Ontslagbrief of overdracht voor verpleeghuis / thuiszorg / ander ziekenhuis is geschreven	O	O

Datum: …… Naam en paraaf verpleegkundige:……..

15.8 Decision tree



AT is defined as a commercially available assistive technology device of which the usefulness has been proven, ranging from simple communication devices (e.g. buttons) to dynamic systems, with control options such as puff-sip switches, eye trackers or mechanical switches.

A usable solution is defined as a device that offers a significant improvement in the communicative abilities of the patient, which is used by the patient on a regular basis and which is considered satisfactory by the patient.