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DECODER

"Deployment of Brain-Computer Interfaces for the Detection of Consciousness in Non-Responsive Patients"

Collaborative Project
Information and Communication Technology

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PP Restricted to other programme participants (including the Commission Services)
RE Restricted to a group specified by the consortium (including the Commission Services)
CO Confidential, only for members of the consortium (including the Commission Services)

STANDARD ETHICAL GUIDELINES WRITTEN AND DELIVERED TO ALL PARTNERS

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Abstract

This paper describes in detail the standard ethical guidelines relevant for the DECODER project. The aims of DECODER are to develop a neurophysiological test battery and brain-computer interfaces (BCI) for the detection of consciousness in non-responsive patients who are otherwise only little or not at all able to interact with their environment. Therefore the core feature of this paper is to define the basic ethical principals that must be taken into account by all partners of the DECODER project when dealing with non-responsive patients. Non-responsive patients' risks and benefits of participation in the studies will be outlined and issues regarding informed consent and optimal data protection will be described meticulously to give the partners concrete advice on how to deal with these patient groups. Finally, we will provide a template of an informed consent form that contains all relevant ethical issues concerning DECODER studies. This template will serve as a check-list for all DECODER partners and should be included in the local ethical reports.

Content

1 Introduction

1.1 The population: Non-responsive patients

Each year, a large number of people are diagnosed with a disorder of consciousness (DOC). Among the DOCs, those of interest in DECODER (see list below) represent the most severe forms since they may lead to a non-responsive state in which no communication is possible between the patient and other people or the environment.

Non-responsive people included in the DECODER project:

- Vegetative state (VS), e.g. after traumatic brain injury, stroke, or anoxia.

- Minimally conscious state (MCS), e.g. following traumatic brain injury, stroke or anoxia.

- Locked in state (LIS), e.g. after traumatic brain injury, stroke, or anoxia, or degeneration of the motorsystem.

- Healthy subjects undergoing anaesthesia with propofol (WP5 only). These subjects are of course no patients, but will be in the same state due to sedation with propofol.

Healthy controls included in the DECODER project:

Experiments in humans proposed in DECODER will be further carried out with adult healthy volunteers to ensure initial evaluation of the proposed paradigms and BCI systems used within DECODER and to obtain immediate feedback about the efficacy of the proposed DECODER approaches.

For patients with disorders of consciousness (DOC) like vegetative state (VS) and minimally conscious state (MCS) non-responsiveness is a criterion for diagnosis of the disease. Regarding locked in state (LIS), awareness and consciousness may be preserved but these patients cannot move or communicate due to complete paralysis of nearly all voluntary muscles in the body. Therefore misdiagnosis is exceptionally high in patients with LIS. Patients with severe disorders of consciousness present a great challenge to standard diagnostics since the non-responsiveness of such patients implies that they can only be diagnosed by means of exclusion criteria like “no goal-directed eye movement” or “no execution of commands”.

1.2 The Character of the DECODER studies

1.2.1 Aims, paradigms and methods

The main aims of DECODER can be summarized as followed: The first aim is to develop a neurophysiological test battery for the detection of consciousness in non-responsive patients. The test battery will greatly improve standard clinical diagnostic routines because it allows for the investigation of participants’ brain functions both at rest and in response to different sensory stimulations or instructed provocations by means of non-invasive methods in the absence of overt motor or behavioral responding.

The second aim of DECODER is to provide non-responsive patients who proved to be consciously aware but unable to perform any motor movement with a means of communication and interaction. Such a means must not rely on any motor input. Brain computer interfaces (BCI) constitute such a non-motor dependent means of communication.

The stimulus material used in DECODER will include visual, auditory and fibro-tactile stimuli comprising simple stimuli (e.g. light-flashes, tones) as well as more complex semantic stimuli such as words and sentences including participants' own name or pictures displaying human faces or concrete objects. All stimulation procedures used in DECODER will be non-painful to the participant. Neurophysiological methods will include non-invasive techniques such as EEG, fNIRS and fMRI.

As described in detail in the annex of Decoder both, stimulations and neurophysiological recordings will be conducted with CE certificated instruments that meet the consumer safety, health and environmental requirements of the European commission.

Nevertheless, when applied in non-responsive individuals the DECODER approach may challenge basic ethical principles typically postulated for research with healthy subject populations. These ethical challenges and questions will now be addresses in detail.

2 Ethical aspects

2.1 General principles - Informed consent

To protect fundamental rights in medical treatment and research, informed consent has been established as the gold standard to respect and protect fundamental human rights in medical treatment and research in healthy subjects and clinical patients. The fundamental aspects of informed consent relevant to scientific research activities are documented in international conventions, declarations and codes of conduct such as the Declaration of Helsinki launched by the World Medical Association (WMA) in 1964, the Charta of Fundamental Rights that holds for all European countries as well as the European Council's Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine (Convention on Human Rights and Biomedicine), to name but a few of the international and european ethical guidelines that will be respected in the DECODER studies.

In summary, these conventions suggest that *"any intervention in the health field may only be carried out after the person concerned has given free and informed consent to it. This person shall beforehand be given appropriate information as to the purpose and nature of the intervention as well as on its consequences and risks. The person concerned may freely withdraw consent at any time* (see European Council's Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine" (cited from the Convention on Human Rights and Biomedicine, fifth article).

2.2 Ethical aspects particularly relevant for research in non-responsive patients

With DECODER we are addressing non-responsive individuals who, by definition will not be able to give voluntarily informed consent to participate in the DECODER studies. All members of the DECODER consortium are well aware of the specific ethical situation concerning research in non-responsive patients.

The unique experience of the DECODER consortium with non-responsive patients and ethical issues will however ensure procedures according to highest ethical standards as outlined in

- The Charta of Fundamental Rights of the European Commission.

- The Directive 2001/20/EC of the European Parliament and the Council regarding good clinical practice in the conduct of clinical trials on medical products for human use.

- The Directive 95/46/EC of the European Parliament and the Council (24.10.1995) on the protection of individuals with regard to the processing of personal data and on the free movement of such data.

- The Council Directive 83/570/EEC (26.10.1983) amending Directives 65/65/EEC, 75/318/EEC and 75/319/EEC on the approximation laid down by law, regulation or administrative action relation to proprietary medicinal products.

- The Convention on the Council of Europe on Human Rights and Biomedicine (04.04.1997)

- The Helsinki Declaration in its latest version (sixth revision, 2008) developed by the WMA for the medical community regarding human experimentation.

In the annex of DECODER the consortium members have already proposed precise standardized procedures on how to deal with non-responsive patients in the DECODER studies. These suggestions are based on the extensive experience of the DECODER consortium in the field of ethics in science and research in non-responsive patients and will be obligatory for all DECODER partners who will run studies with non-responsive patients (UT, UW, TUG, FSL, ULG, and MRC).

These standards proposed by the DECODER Consortium are summarized below and sorted according to major ethical aspects.

2.3 Ethical guidelines and standards for the research in non-responsive patients developed by the DECODER consortium

1.) **Approval of the local ethics committees:** The local ethic committees will be informed about the DECODER studies. Ethic approvals will be obtained before the start of the DECODER projects and thus before any experiment/study is conducted. Besides the general ethical issues discussed in this paper that apply to all DECODER partners, each DECODER partner (i.e. the work package leaders) has to take care that ethical issues will strictly follow the law of the country and the local medical institutions in which the particular examination will be performed. The DECODER partners will not be allowed to carry out any study without a documented informed consent to protect participants as well the responsible DECODER staff from being accused on the basis of criminal law for committing crimes against the life, or the physical and mental integrity of the subjects in case of complications during or after the studies.

2.) **Ethical Management:** Adherence to the principles of the ethical committee review board will be monitored by the DECODER Program Management Team (PMT), who will ensure that documentary evidence of ethical approval is obtained for all contracting DECODER partners investigating non-responsive patients and healthy controls. A copy of each application to the local ethic committee and the informed consent applied in the studies will be collected by the PMT to allow the DECODER Steering Committee an overview that each study performed within DECODER will be conducted according to ethical standards relevant for DECODER. Any complaints or adverse incidents regarding DECODER studies will be reported to the PMT and the Steering Committee and immediately referred to the local ethical committee that approved the research, to allow for independent review and appropriate disciplinary action if necessary.

3.) **Informed consent:** Regarding informed consent of non-responsive patients DECODER will ensure that the legal representatives of the patients will be informed in detail about the purpose, goals and procedures of the DECODER studies according to standard Ethical guidelines (see §4 Directive 2001/20/EC). Information will be provided in written form as well as verbally by the responsible experimenter of the DECODER studies. When no legal representative of a non-responsive patient is personally available, the legal representative(s) will be contacted via telephone and by mail to inform about the study by the doctor or researcher who is in charge of the patient. The legal representative(s) will be given sufficient opportunity to read the information and ask questions concerning the studies (including risks and benefits). They will be informed that participation is completely voluntary, that there will be always the possibility to terminate the study without providing reasons and that no disadvantage will arise from leaving the study. Benefits of participation in the studies but also any risks associated with participation will be explained (see in detail 2.5.). The legal representative(s) including the treating doctors and staff will be well informed about the experimental nature of the DECODER studies. This means that they are informed that by participation in DECODER no decision or conclusion can be drawn regarding questions of life-sustaining treatment in non-responsive patients including medical treatment or therapeutic interventions in non-responsive patients. All this information will be given before the legal representative(s) of the patient gives his/her written informed consent. In addition, written informed consent of the legal representative(s) must be given prior to the patient's participation in the study. In addition, before each neurophysiologic testing phase the legal representative(s) of the patient will have the opportunity to indicate if participation in the study is still wanted. If consciousness is detected and patients are able to respond by means of BCI, patients will be asked directly whether they would like to continue with the procedure.

4.) **Safety aspects:** Regarding non-responsive patients the safety of the participants is a primary objective of the DECODER studies. The staff and researchers involved in the DECODER studies will comply with safety procedures. The option of expert safety officers will be sought wherever appropriate. General safety procedures will be implemented for all stimulation procedures, fire safety and other general issues. All procedures involving devices such as electrical equipment (e.g. handheld computers) will be subject to standard safety review (see annex for details). Patients and healthy controls involved in the project will not be exposed to unnecessary risk, which will be assessed as part of the ethical approval, general health and safety assessment and monitoring. Ample insurance liability will be contributed by each participating centre for its own procedures.

Specific safety protections in non-responsive patients: In practice, the present research is non-invasive and safe. Nevertheless, regarding non-responsive patients specific safety protections will be carried out to reduce any distress and discomfort of the patients during the experiments. Specific attention will be paid to the experimental setting: Peripheral-physiological measures (heart rate, breathing, skin conductance) will be recorded throughout the experiment (all mandatory for fMRI; for EEG heart rate monitoring is sufficient). These measures are highly sensitive to stress and ensure that the patients are comfortable throughout testing. An additional person will be in charge of solely monitoring the patients. This person will not be involved in the experiment so that we can ensure undivided attention for the patient. Throughout experimental testing a medical doctor and/or nurse will always be immediately available. Patients will be tested only when there are grounds for assuming that the direct benefit to the patient outweighs the risks (see §4 Directive 2001/20/EC). Therefore, DECODER has defined clear inclusion/exclusion criteria which individuals can and which cannot be recruited as participants (see issue 2.4. below for details). The legal representatives as well as the

treating doctors will be informed about the safety aspects as well as the inclusion and exclusion criteria to reduce potential risks for non-responsive patients to participate in the study. The legal representative(s) will be asked to give written informed consent that they have been informed about the safety aspects and the inclusion/exclusion criteria.

5.) **Test bed propofol in healthy volunteers:** Regarding healthy subjects undergoing anaesthesia by light sedation with propofol only healthy volunteers are allowed to be included in the study and informed consent and a thorough general anamnesis by a medical doctor is the prerequisite for the participation in the study. The substance will be delivered by an anaesthesiologist who will be present throughout the experiment and control any changes of the vital functions (heart rate, CO_2 in the breath). Any fluctuations in vital parameters will cause an immediate stop of the experiment. In the very rare event of serious complications, care is taken that participants will be transported to the short distanced clinics. As in non-responsive patients, healthy volunteers will be informed in detail about the background, objectives, and possible risks of the study.

6.) **Data protection:** Background data of participants will have to be collected. In non-responsive patients these will include age and gender as well as disease related data such as diagnosis, duration of the disease, cause of the disease or medication that could affect the brain. DECODER will take care to ensure that confidentiality of personal information is not breached between family members or partners. Healthy volunteers who will take part in the test bed propofol studies as well as healthy participants that will take part in the DECODER studies as controls will be asked about neurological, psychiatric or somatic diseases or any other diseases, habits or medical treatment that could affect the brain. All personal data and information relating to an individual's health, ethnicity, gender or age will be stored and handled according to the principles of data protection. In practice this means that individual data will be anonymised for research purposes, written material will be stored in secured locations and the recoded data stored on computer will be protected by password and encoding (SSL-technology). Any publication derived from personal data will be presented in a way that makes it impossible to identify individuals.

After the experiment participants (healthy volunteers) as well as the legal representative(s) of the non-responsive patient will be informed about the results. Regarding non-responsive patients the results will be referred to the doctors if the legal representative agrees. Each researcher involved in DECODER including the treating doctor and staff will agree by signature to treat patients' results confidentially.

7.) **Media coverage:** Regarding the final aim of DECODER, media presence is a very important issue for the dissemination of the DECODER products (diagnostic test battery and single switch BCI development for communication use in non-responsive patients). Media presence is also important for keeping the people in need up-to-date about our products. All members of the consortium are constantly approached by media, highly experienced in dealing with media, and regarding ethics well aware of the necessity to protect privacy of patients, their families and other people involved in the project. If patients will be part of a media report, specific informed consent has to be provided by the patients or his or her legal representative. In this informed consent it will also be specified for which specific medium the specific report will be produced. Only for this one specific report the patient will consent. Regarding media coverage only general information about the background and objectives of DECODER will be provided. Details about patients and software/hardware development will not be disclosed. Whenever the journalists wish to use the report for another medium they will have to get the consent of the

participants or in case of non-responsive patients of the legal representative(s). Journalists will also be required to provide a short description of the content and objective of the report to ensure that it can be made explicit to the patient/legal representative. The media related informed consent will be written with the support of the legal administration of each of the Universities.

2.3.1 Inclusion and exclusion criteria for participants to take part in the DECODER studies

Non-responsive patients at clinics or research centres of the DECODER consortium members for diagnostic or therapeutic reasons, at nursing homes, rehabilitation clinics and at home will be included in the study. Healthy volunteers including controls will be recruited by UW, UT, FSL, TUG, UM, MRC and those participating in the test bed propofol research will be recruited via advertisements by ULG.

In the Annex DECODER has defined clear inclusion/exclusion criteria mentioning which individuals can and which cannot be recruited as participants.

2.3.2 Diagnostic battery and BCI studies

Regarding the ***diagnostic battery*** and ***the BCI studies*** inclusion criteria for non-responsive patients to take part in the studies are above 18 years of age. Exclusion criteria for not admitting a patient or healthy controls to take part in the DECODER studies are individual factors and circumstances that prevent proper EEG-, fMRI- or fNIRS- signal acquisition such as

- skin contamination,
- wound on scalp,
- dermatitis or medication that affect the central nervous system,
- virus infections, including MRSA or other virulent diseases including Hepatitis A/B/C

Patients who suffer from chronic infections such as MRSA will not be included in the studies. Moreover, only healthy people not suffering from virus infections or any inflammatory autoimmune or chronic somatic diseases (e.g. Hepatitis A,B,C) will be allowed to conduct the studies to protect the health of both patient and researcher. Standard cleaning and sterilizing of equipment (e.g., EEG caps) will be applied.

- Pregnancy
- uncontrolled, gross muscular activity,
- Patients who appear clearly hyperkinetic and unlikely to remain sufficiently still throughout the recording sessions will be excluded when such a situation is evident at the day of testing.
- If potential participants are on medication that affects the central nervous system, then a further investigation is necessary to find out whether the medication alters the EEG- or bold-signal (fMRI/fNIRs) to such an extent that results of the diagnostic battery or BCI cannot be interpreted.
- Regarding fMRI, additional exclusion criteria for patients are paramagnetic medical apparata that may not be suitable for being entered in the fMRI environment. Similarly healthy volunteers (controls) will be excluded from taking part in the fMRI studies when they have metal in their body (this includes plates or screws from surgery, unremovable metal piercings or permanent retainers; dental fillings are OK).

If a patient is released from the clinics/therapeutic centres of the consortium members before all measurements requested for the study are performed, the legal representative(s) will be informed that measurements can be continued at the next visit. Otherwise, they will be offered to get an additional transport to the clinics/therapeutic center paid by the consortium member.

2.3.3 Test bed propofol

Regarding the **test bed propofol studies** inclusion criteria for healthy volunteers to take part in the studies are above 18 years of age. Exclusion criteria are the same as for all healthy volunteers plus a set of criteria proper to anaesthesia. They will have general medical anamneses including a check on cardio-vascular, pneumonal and neurologic functions. A blood sample will be taken to check for biological abnormalities (cellular, ionic or plasmatic) or infections (HIV and hepatitis B). They will also be checked for MRI counter indications. Women will be excluded if they do not use any contraceptive. All women will have a urinary pregnancy test one week before the experiment. Subjects won't have a history of brain trauma or neurosurgical operation, psychiatric trouble, substance abuse, asthma, motion sickness or previous anaesthetic complications. Subjects will be recruited in the medical population (i.e., medical and nurse students) to be fully aware of the anaesthetic risks. Subjects will be on diet for at least 6 hours before the experiment.

2.4 Benefits and risks for non-responsive patients

2.4.1 Benefits

Non-responsive patients have a great potential to benefit from participation in DECODER: Neither the passive nor the active diagnostic paradigms are yet included in routine clinical diagnosis of non-responsive patients. Based on the available technology and additional research a tremendous progress could be made toward establishing approaches to unequivocal diagnosis for the benefit of the patients. BCI technology as a part of such a diagnostic battery would bridge the gap between passive and active diagnosis and functional communication.

2.4.2 Risks

Patients and their relatives as well as the legal representative(s) including the treating doctor and staff may however have unrealistic hope in terms of curing and recovery from the disease when they accept patients with DOC to participate in the DECODER studies. To keep expectations as realistic as possible, the patient's legal representative(s), the treating doctor(s) and staff will be explicitly informed about

a) the possible outcomes of the diagnostic battery and
b) the use of BCI in non-responsive patients
c) the timeline of different measurements and about the outcome of the testing.

Additionally, we have to deal with the possibility that non-responsive patients who proved to be consciously aware will communicate the wish to die when being provided with a BCI. If this were the case, the following steps will be undertaken:

1. The communicated wish to die would be ascertained in follow-up sessions.
2. The patients' doctors and significant others would be informed, provided the patient consented.
3. The patient would be thoroughly interviewed to find out if he or she is depressed. Depression is often associated with suicidal thoughts and completed suicide. If a patient was diagnosed with major depression, this psychological disorder would have to be treated. Thus a consultation of a psychiatrist will be necessary. If a patient is diagnosed with major or reactive depression, this psychological disorder will have to be treated.
4. If the patient were not or no longer depressed and would still ask for a hasten death, the reasons for this wish would have to be thoroughly explored. Expected poor quality of life, the fear of pain, and the fear of being a burden for the family are the most frequent reasons for the wish of a hastened death by patients with fatal disease. All these issues can be addressed and eliminated. Research

done by the DECODER partners shows that patients in all states of physical disease can experience a good quality of life; pain can be well treated with medication and professional caregivers can help the family to care for the patients.

5. If all these reasons can be excluded as the reason for the wish to die, the patient together with his or her significant other and doctors have to decide on further steps to be undertaken in accordance with national policies.
6. Steps 2 to 5 will not be undertaken by doctors and psychologists in charge who will be informed about the purpose of the studies prior to testing procedure.
7.

3 The Informed Consent Form – A Template for DECODER

From an ethical point of view it is clear, that all DECODER studies that involve human subjects require informed consent of the participants or in case of non-responsive patients of the legal representative(s). Given the wide range of studies and methods used in DECODER and the inclusion of individuals ranging from non-responsive patients to non-responsive healthy participants under anaesthesia (test bed propofol studies) to healthy controls it is clear that in the following no single general informed consent form that can be used by all DECODER partners can be provided.

Thus, all DECODER partners are provided with a template of an informed consent form that serves as a check-list for all DECODER partners. This template will ensure that all studies conducted within DECODER conform to common ethical principles and standards proposed by the DECODER consortium discussed above and therefore guarantees the safety of the participating individuals and the protection of their human right and dignity.

As mentioned before, all partners of DECODER are experts in their field of research and have long-standing experience in the research with non-responsive patients. It will be the responsibility of each of the DECODER partners to ensure that research within DECODER is conducted according to standard ethical guidelines and the ethical principles proposed by the DECODER Consortium (see issues 2.2 and 2.3.). It is their responsibility to ensure that informed consent will be applied to all participants taking part in DECODER and to inform the local ethic committee about the DECODER research. It is their duty to contact the local ethics committee as well as the DECODER Consortium if any problems regarding ethical aspects arise during their studies to guarantee rapid solutions for these problems and protection of participants' health. In addition, each DECODER partner will ensure that a copy of the application to the local ethic committee including the informed consent form will be send to the PMT.

3.1 The content of the form

Regarding the content of the informed consent form the following points must be included to ensure standard ethical guidelines regarding research in human subjects (see issue 2 in this paper). Some of the sections listed below, like data protection and the statement of voluntary participation and of the right to withdraw from the study, are mandatory. The issues to be mentioned in the form will be fewer in case of healthy volunteers, and more in case of non-responsive patients (including healthy volunteers who take part in the test bed propofol studies).

Each DECODER partner will use the template as a check-list to develop an informed consent form for their particular studies in their own language. In general, the informed consent form must be written in comprehensive text and will entail three parts: **Part I** (General Information regarding the aims of Decoder), **Part II** (Detailed Information regarding the aims, methods and scope of the studies for which informed consent will be taken) and **Part III** (The Consent including the statement of consent signed by the participants or their legal representative(s)).

3.1.1 Part I: General information

The first part will inform the potential participant or the legal representative(s) of the non-responsive patient about the general purpose of the DECODER project as stated in the seventh framework programme of DECODER. Here, the experimental and non-invasive nature of DECODER will be pronounced and the reader will be informed that participation is completely voluntary and that refusing participation will have no negative consequences on participants' health or medical treatment and therapeutic interventions in non-responsive patients. Regarding non-responsive patients the main information given in PART I will already include a basic description of inclusion and exclusion criteria for patients to participate in the study to keep expectations of the legal representative(s) who will decide on the patient's participation as realistic as possible. Finally, it will be mentioned how participants can participate in the studies and who to contact in case of further questions. The telephone number and/or email of the person who is in charge of the experiment will be provided. The informed consent form will also include the following information:

- the title of the project to which the present study/ies belong to (i.e. DECODER)
- the funding institution (i.e. European commission)
- the title of the particular project
- the principle investigators including name, address, phone number and email
- the name of the person to contact for further information (name, address, phone and email).

Regarding studies in non-responsive patients, information presented in PART I will also be distributed to the treating doctors and staff.

3.1.2 Part I: Detailed information

In the second part of the informed consent form, the participant or the legal representative(s) of the non-responsive patient must be informed in detail about the purpose, the procedure, the methods (EEG, fNIRS, or fMRI), the safety aspects and the risks of the specific experiment(s), he or she will participate. In addition, he/she will be informed about formal rights and data protection.

The following questions will be answered for the participants in part II:

1.) Which study I might take part in?

2.) What does participation involve? Time and effort.

3.) What benefits of participation can I expect?

4.) What risks, inconveniences and discomforts of participation are possible?

5.) Is participation safe? What safety protection procedures do exist?

6.) Do I need support by others?

7.) Can I withdraw from participation?

8.) Are there preconditions for participation?

9.) Are my data protected?

Ad 1.) Which study might I take part in? A detailed description of the procedure of the study/ies will be provided in comprehensive text. The stimulation procedure and the neurophysiologic recording methods used in the studies will be described in detail. Safety protection issues will be outlined whenever necessary. Regarding neuroimaging studies it will be mentioned that even in healthy controls the imaging procedure will not be used to identify or diagnose structural brain deficits, but should mention the possibility of occasional diagnoses and how to deal with this kind of information.

Ad 2.) What does participation involve? It will be stated what participation in the study requires from the participants in terms of time, individual resources and effort. It will be stated explicitly how long the current experiments last including preparation time for e.g., scanning or correct electrode/optode placement on the participant's head or application of the sedation agent propofol and if recordings will be done on a single day or require multiple testing across days. It will be mentioned that in experiments with non-responsive patients in the latter case legal representatives will be informed about each recording session. If participants will receive a compensation for participation this will be explicitly mentioned here and if so, it will be comprehensive for the participants when it is paid (prior to the study or at the end).

If participants including non-responsive patients take part in different studies written informed consent is required from this particular individual or the legal representative(s) for each of these studies.

Ad 3.) What benefits of participation can I expect? It is important to mention that participants may not benefit directly from the study. Regarding non-responsive patients, it is important to point out that participation in the studies does not ease the disease nor allows for predictions about medical treatment/therapeutic interventions or decisions on life-sustaining treatments (see issue 2.3.) It will be clearly stated that DECODER studies aim at developing a diagnostic test battery/ BCI prototypes that are currently not available on the market and must be evaluated and tested before they can be routinely used by the public and in clinical routines. Again the experimental nature of the experiments will be stressed and become transparent to the participants. It should be pointed out that by participation in the experiments/studies, individuals could in the long run help to facilitate a better understanding of altered states of consciousness (also applies to the test bed propfol studies) and improvement of diagnostic routines and communication in non-responsive patients with diseases of consciousness.

Ad 4.) What risks, inconveniences and discomforts of participation are possible? It will be ensured that all possible risks, inconveniences or discomforts that may appear during the study participation are stated (for details see issues 2.2 and 2.3 in this manuscript). It must not be forgotten to mention that all stimulation procedures, methods and devices used in the studies will be conducted with CE certificated instruments that meet the consumer safety, health and environmental requirements of the European commission (see issue 1.2.1. and annex). It should be mentioned that up to now there have been no reports on any negative side-effects of the stimulation procedures and/or the non-invasive BCI technology used in the DECODER studies. Regarding test bed propofol studies the potential risks as outlined above and in the annex must be stated in detail.

Ad 5.) Is participation safe? What safety protection procedures do exist? It should be described in detail what safety protection procedures will be applied to ensure participants' health and comfort (see issue 2.3. in this paper).

Ad 6.) Do I need support by others? It should be mentioned if during the experiment and/or recording session support by others (e.g. doctors, researchers or clinical staff) in charge of the patient/participant or the study) will be given, by whom it is given and in which form.

Ad 7.) Can I withdraw from participation? It is mandatory to mention, that participation in this research is voluntary, that individuals who decide to take part in the experiment are free to withdraw their consent at any time during the experiment without any explanation and that the decision to withdraw will have no personal negative consequences nor will it in case of non-responsive patients have any negative consequences on medical or therapeutic treatment. You also have to state that for non-responsive patients, the decision to not take part in the study will not influence the relationship between the participant and the treating staff of the hospital.

Ad 8.) Are there preconditions for participation? Here, you should describe in detail the factors that are prerequisite for study participation including exclusion and inclusion criteria stated above in issue 2.4. Please also mention if individuals may take part in a selection and screening procedure prior to the actual beginning of the studies. This might be the case in the test bed propofol studies but also in experiments with non-responsive patients to find out if successful acquisition of adequate brain signals is possible at the day of testing or if patients can underwent functional imaging without any risks (see issue 2.5.).

Ad 9.) Are my data protected? It will be described in detail how individual data will be protected. Here the following aspects must be mentioned:

1.) Any information that is obtained in connection with this experiment/study will be treated confidentially and will be disclosed only with the permission of the participant /legal representative(s). Information will be coded. Only the researchers will know the code and will keep this information under strict control.

2.) No one but the researchers will be able to see information regarding the experiment/study and the information will not be shared with or given to anyone [except that the participants or the legal representatives agrees with this].

3.) In some cases of legally highly regulated studies, an exception is necessary, as the law might demand a report of results to a ‘competent authority’. In that case, this has to be stated in the consent form.

3.1.3 Part III: The consent

Part three contains the formal and final consent to participate. This is the actual contract and must contain at least the following statement.

Statement of consent:

I herewith certify that I have read and fully understood the information given above. I agree to take part in the selection procedure for [...]. I am aware of my rights, especially my right to have my data protected and to withdraw my participation at any time. In case of withdrawal I do not have to declare any reasons nor will my withdrawal lead to any disadvantages. This consent is given voluntarily, without coercion or undue influence.

I will be given a signed and dated copy of this consent form. The Consent must include the Name and Signature of the Patient / legal representative(s), the signature of the Principle Investigator, including date and location.

4 Conclusion

In this paper the standard ethical guidelines relevant to all Decoder partners were explained in detail. Special emphasis was laid on the investigation of non-responsive participants. A systematic description was provided how to ensure research in these patient groups according to general ethical principles and well grounded ethical suggestions of the DECODER consortium. The most significant issues relevant for DECODER were stated in detail. Finally, an informed consent template for the DECODER project was provided as a direct support of the DECODER partners.