Title Page

Protocol Title: EEG-based depth of anesthesia monitoring – effects on wake-up times and cognition.

Protocol Number: 32173 ver. 2.0

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Collaborator: Anders Aasheim PhD Fellowship

Sponsor Name: Oslo University Hospital, Akuttklinikken v Øyvind Skraastad

Regulatory Agency Identifier Number(s)

REK 32173

Approval Date: 14.11.2019

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Table of Contents

1. Protocol Summary

1.1. Synopsis

Protocol Title: EEG-based depth of anesthesia monitoring – effects on wake-up times and cognition.

Short Title:

Rationale:

Depth of anesthesia-monitoring (DoA-mon) based on EEG changes demands knowledge about the effects of the different anesthetic medications on EEG waveforms. We want to investigate the use of the raw-EEG waveform in addition to indexes (BIS) and EEG spectrogram analyses for depth of anesthesia monitoring. We hypothesize that with the use of this monitoring, we will be able to better individualize the dosage of anesthetic drugs, and that this will reduce the total consumption of anesthetic medication, thus reducing time to wake-up after surgery. Some studies have indicated that too deep anesthesia, confirmed by "burst-suppression" or isoelectric-EEG, is associated with increased postoperative cognitive dysfunction (POCD). We will therefore assess the patients with the Cambridge Neuropsychological Test Automated Battery (CANTAB) cognitive function assessment tool.

Objectives and Endpoints

Objectives	Endpoints
Primary	
• Use of DoA-mon reduces anesthetic dosage and wake-up times	• Total amount of propofol (mg/kg/hr) administered • Time to wake-up after halt of anesthetic administration
Secondary	
• Use of DoA-mon reduces POCD	• Cognitive functioning

Overall Design

Disclosure Statement: This is an interventional study. The study has two arms, and is single blinded for the participant, and assessment masked for the investigator. It is blinded for the post-operative care providers.

Number of Participants:100

Approximately 200 patients will be screened to achieve enrolled to study intervention and 100 evaluable participants for an estimated total of 50 evaluable participants per intervention group.

Intervention Groups and Duration:

Perioperatively guiding depth of anesthesia by EEG-based monitoring, assessed preoperatively 1 day before surgery, and at 3 hours, and at 24 hours after surgery.

Data Monitoring :

Yes, by clinical trial units monitor Jacob Jacobsen.

1.2. Schedule of Activities (SoA)

Procedure	Screening (up to 14 days before Day 1)	Intervention Period Days/Hours				
		–1	**1 directly prior to surgery**	**1 / 3 hrs after surgery**	**2 / 24 hrs after surgery**	Comments
Informed consent	X	X				
Inclusion and exclusion criteria	X					
physical examination	X					**Standard preoperative/anesthetic assessment**
Height and weight		X				
Medical history	X					
Vital signs		X	X	X		
Pain and sedation level assessment		X	X	X	X	**VAS scale/RASS sedation score**
Randomization			X			
Study intervention			X			
CANTAB cognitive assessment	X			X	X	
AE review				**X**	**X**	

2. Introduction

Depth of anesthesia-monitoring based on EEG changes demands knowledge concerning the effects of the different anesthetic medications on EEG waveforms. We want to investigate the use of the raw-EEG waveform in addition to indices (BIS) and EEG spectrogram analyses for depth of anesthesia monitoring. We hypothesize that with the use of this monitoring, we will be able to better individualize the dosage of anesthetic drugs, and that this will reduce the total consumption of anesthetic medication, thus reducing time to wake-up after surgery. Some studies have indicated that too deep anesthesia, confirmed by "burst-suppression" or isoelectric-EEG, is associated with increased postoperative cognitive dysfunction (POCD). We will therefore assess the patients with the Cambridge Neuropsychological Test Automated Battery (CANTAB) cognitive function assessment tool.

2.1. Study Rationale

To investigate options to individualize anesthetic dosage based on the EEG-responses to hypnotic drugs during general anesthesia. This to potentially reduce total amount of anesthetic drugs administered, and henceforth possibly reduce postoperative cognitive dysfunction after surgery and anesthesia.

2.2. Background

It has been over 80 years since Gibbs et al (1) showed how the electroencephalogram (EEG) systematically changed in concurrence with increasing doses of hypnotic drugs such as penthobarbital and Ether. The study concluded that "Electroencephalography may therefore be of value in controlling depth of anesthesia and sedation". In spite of a solid documentation of the systematic connection between dosing of anesthetic drugs, EEG-patterns and level of sedation/anesthesia (2-8), EEG-based DoA has not become a part of standard of care in anesthetic management. There is abundant evidence of how different anesthetic drugs leads to characteristic fluctuations in human brain electrical activity, relating to depth of anesthesia, anesthetic drug of choice, and age (7,8,9-15). These anesthetic induced fluctuations are readily visible as changes in the patients EEG.

Anesthetic drugs are usually administered in pharmacological models based on a population taking into account their age, weight and height. However, there is a significant difference in how patients respond to these models. In adults there is evidence that the doses needed to achieve consciousness varies with a factor of 2 above and below suggested doses (20). In under-dosing of anesthetics there is a risk of peroperative awareness (21,22). On the other hand there is also evidence that overdosing of anesthetics has harmful effects; children receiving more than 4% Sevoflurane can demonstrate epileptiform activity (23,24), and adults overdosing into "burst suppression" during anesthesia has a higher risk of postoperative delirium (POD) and increased occurrence of postoperative cognitive dysfunction (POCD) (25,26).

Bispectral Index (BIS) is an algorithm developed by Aspect Medical Systems in 1994, which is based on weighted sums of EEG subparameters to present an index from 0 to 100 for depth of anesthesia, where 100 is wide awake, and 0 is an isoelectric EEG. The BIS target for a deep

enough anesthesia is set to be between 40 and 60. The BIS number is often in concurrence with other clinical observations related to anesthetic depth, however there is also an experience of divergence. BIS and other EEG-based indices are programmed from adult cohorts, and cannot be directly trusted in children, or the elderly (29,30). There is also an incapability in these preprogrammed indices (BIS and other) to integrate how specific anesthetic drugs affect the EEG, and thenceforth the BIS value. An example of this is how the drug Ketamine induces a specific gamma-frequency in the EEG, which the BIS-index translate as a lighter anesthesia, even though the drug is administered "on top of" an already deep level of anesthesia.

2.3. Benefit/Risk Assessment

The benefit for the participants in this study is an increased attention from the anesthetic staff, and that the monitoring of levels of anesthesia will be standardized and thorough regardless of which study-group you wind up in. The risk of awareness during surgery is what we always achieve to avoid, and the risk of this is low in both study-arms. We will screen for this after surgery; all patients will be interviewed to assess their experience of the procedure, what they remember and overall satisfaction with our treatment.

Both arms of the study represents ways of delivering general anesthesia in surgery today. The incindence of awareness in North America and Europe is 1 to 2 cases/1000 (45-50). A 2019 meta-analysis of randomized trials compared BIS-EEG guidance of anesthetic depth to reduce the risk of awareness from 9 to 3 pr 1000 (51). So there is a small possibility that the intervention reduces the risk for awareness for the participants in this study.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
• Use of DoA-mon reduces anesthetic dosage and wake-up times	• Total amount of propofol (mg/kg/hr) administered • Time to wake-up after stop of anesthetic administration
Secondary	
• Use of DoA-mon reduces POCD	• Cognitive functioning

4. Study Design

This is a randomized controlled blinded study, with two groups; intervention and control.

4.1. Overall Design

Both groups will receive standard of care in total intravenous anesthesia (TIVA), with onitoring of clinical signs relating to level of anesthesia and to the satisfaction of the surgeon. In the intervention group, the anesthesia providers will guide the dosage of hypnotics based on a BIS-index of 45-60 perioperative, also avoiding burst-suppression (visually detected)/suppression-ratio (SR) of 0, and EEG-frequency alpha (peak alpha) of 10-12 hz.

All patients will have a recording of their perioperative EEG. All patients will be assessed pre and postoperatively using the Cambridge Neuropsychological Automated Test Battery (CANTAB) to assess how they are affected , testing for executive cognitive functioning. The participants use an IPAD to self-assess, so the assessor is blinded.

4.2. Scientific Rationale for Study Design

4.2.1. Participant Input into Design

We seek to include patient representation, not in study design, but in the design/text of the participant information leaflet.

4.3.1 End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including the last assessment on day 2 of surgery.

The end of the study is defined as the date of the last visit of the last participant in the study.

5. Study Population

Patients coming to Oslo University hospital Rikshospitalet, for planned elective spinal surgery.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

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Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. Participant must be 18 to 65 years of age inclusive, at the time of signing the informed consent.

Sex

2. Male and/or female

Informed Consent

3. Capable of giving signed informed consent as described in Appendix 1 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

4. Psychiatric disorders
5. Pregnancy
6. Breast feeding
7. Using antiepileptic drugs.
8. Central neurological disease
9. Unable to complete baseline CANTAB-test.

6. Study Intervention

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1. Study Intervention(s) Administered

EEG-based DoA-mon, Bilateral BIS from Medtronic, to help guide dosage of anesthetic medication perioperatively.

6.1.1. Medical Devices

1. The manufactured medical device provided for use in this study is the Bilateral BIS by Medtronic. Electrodes are purchased by the hospital, and the medical device company is not a part of this study.

6.2. Measures to Minimize Bias: Randomization and Blinding

Included patients randomized blindly	On the day of surgery, the participants are randomized by an outside party to intervention or control group. The patient is blinded to allocated group. All patients are connected to EEG-BIS before sleep, and EEG-device is covered up (for control-group) after they are asleep. Cover is removed before wake-up. Anesthesia providers are masked from assessing outcome. Investigator is masked from assessing cognitive function through patient “self-assessing” using IPAD software.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue (definitive discontinuation) study intervention. If study intervention is definitively discontinued, the participant will remain in the study to be evaluated.

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3. Lost to Follow up

A participant will be considered lost to follow-up if he or she is discharged prior to 24 postop assessment, or unable to be approached for assessment at local hospital due to transfer from Oslo University Hospital.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

8.1. Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

8.1.1. Physical Examinations

- Assessment of pain levels
- Assessment of experience during and after anesthesia
- Cognitive assessments using CANTAB IPAD software

8.2. Adverse Events(AE) and Serious Adverse Events(SAE)

There will be a collection of data on adverse events; movement during surgery, serious hypotension during anesthesia (MAP<60) or awareness with recall after surgery, and other events that is related to the anesthetic administration. We will not collect data on events related to the surgery.

8.2.1. Time Period and Frequency for Collecting AE and SAE Information

Data on adverse events will be collected directly after surgery, and on the 2 postoperative visits.

8.2.2. Follow-up of AEs and SAEs

All SAEs, and AEs of special interest will be followed up until resolution, or the event is otherwise explained, or the participant is lost to follow-up.

8.2.3. Regulatory Reporting Requirements for SAEs

- The only unexpected and Seriuos Adverse Event in our planned study, will be the occurrence of awareness with recall after surgery.
- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

9. Statistical Considerations

9.1. Statistical Hypotheses

We anticipate that wake-up happens at mean 15 min, standard deviation 5 min (41-44) in the control group. We hypothesize that there will be an improvement of 20% (3 min) in the intervention group.

9.2. Sample Size Determination

We hypothesize that the intervention will reduce amount of propofol administered by up to 20%, also that wake-up may be reduced from 15 min, SD 5 min – to 20 min SD 3 min. With an improvement of 20%, 80% power and a significance level of 0.05, the study will require 88 patients in total, calculated in a two-sample t-test. To add for margin of error/loss we will include 50 patients in each group, summing at 100 patients in total. Due to a difference in plasma levels of anesthetic drugs in men and women, we will do gender stratification when randomizing, to ensure an equal number of sexes in both groups.

9.3. Populations for Analyses

The following populations are defined:

Population	Description
Enrolled	All participants who sign the ICF
Randomly Assigned to Study Intervention	50-50
Evaluable	All

9.4. Statistical Analyses

The statistical analysis plan will be finalized prior to database lock, and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1. General considerations

9.4.2. Primary endpoint(s)

Medication usage; total amount of propofol used (mg/kg/hr) from start to end of anesthesia.

TCI effect site target at start, and each 10 min interval during anesthesia.

9.4.3. Secondary endpoint(s)

Time to wake-up; from halt of anesthetic drugs to

- extubation (sec)
- Verbal respons (sec)
- Motoric response (show right index finger)(sec)

Medication usage of remifentanil micg/kg/min

Medication usage of inotropes (phenylephrine, norepinephrine)

Cognitive function, assessed with 4 trials in the CANTAB IPAD-tool, preoperative function compared with 3hrs after wake-up, and preoperative compared with 24 hrs after wake-up.

9.4.4. Other safety Analyse(s)

Adverse events

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2. Financial Disclosure

This study is financed in total by the investigator/sponsors hospital; either through the investigators PhD-fellowship program, or equipment purchased by the anesthetic department of said hospital.

10.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR

50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

10.1.4. Data Protection

- Participants will be assigned a unique identifier by the sponsor.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent
- Third party software providers (Cambridge Cognition), will store data from the CANTAB cognitive assessment tests as without name or information which would make the participant identifiable. These results will be stored on extra safe servers belonging to Cambridge Cognition in the UK, accessed only by principal investigator and PhD-fellow in the study-group. The handling of this data is covered in the DAP agreement between sponsor, and Cambridge Cognition.

10.1.5. Committees Structure

Leiv Arne Rosseland, co-supervisor, and responsible for randomization. He will not be in contact with participants in this study.

Luis Romundstad, Principal Investigator, supervisor, and Medical monitor.

Anders Aasheim, PhD-fellow, responsible for conducting inclusion of patients in cooperation with PI, managing day-to day operations of participants, collection of study-data.

10.1.6. Dissemination of Clinical Study Data

10.1.7. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, and provide direct access to source data documents.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 5 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.8. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

- Definition of what constitutes source data can be found in the SoA data list.

10.1.9. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is 15 of February 2020, and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the subject and should assure appropriate subject therapy and/or follow-up

10.1.10. Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2. Appendix 2: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.2.1. Definition of AE

AE Definition
• An AE is any untoward occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. We will only collect AE's from events related to the anestetic administration, not from events related to the surgery.

10.2.2. Recording and Follow-Up of AE

AE
• When an AE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event. • The investigator will then record all relevant AE information in the CRF. • It is **not** acceptable for the investigator to send photocopies of the participant's medical records in lieu of completion of the AE CRF page. • The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE.

Assessment of Causality
• The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE. • A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or

arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE, the investigator **must** document in the medical notes that he/she has reviewed the AE and has provided an assessment of causality.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated to elucidate the nature and/or causality of the AE as fully as possible.
- New or updated information will be recorded in the originally completed CRF.

10.3. Appendix 3: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment [32173 ver 2.0]: (02.01.20)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

This is an amendment of the original protocol sent to, and approved by REK-Helse Sør-Øst, due to a request by the clinical trial unit (CTU) of Oslo University Hospital, in order to make a more precise protocol. This amendment will be sent forwarded to REK after CTU has looked it over.

Section # and Name	Description of Change	Brief Rationale
32173 ver 2.0	Specification of details	

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