# DETERMINATION OF ANALGESIC EQUIPOTENT DOSES OF INHALED METOXYFLURANE VS. INTRAVENOUS FENTANYL USING COLD PRESSOR TEST (CPT) IN VOLUNTEERS: A RANDOMIZED, DOUBLE BLIND, PLACEBO-CONTROLLED CROSSOVER STUDY.

**Protocol Identification Number: 2018-0910-4**

**EudraCT Number: 2018-003939-30**


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# SIGNATURE PAGE

Title DETERMINATION OF ANALGESIC EQUIPOTENT DOSES OF INHALED METOXYFLURANE VS. INTRAVENOUS FENTANYL USING COLD PRESSOR TEST (CPT) IN VOLUNTEERS: A RANDOMIZED, DOUBLE BLIND, PLACEBO-CONTROLLED CROSSOVER STUDY

Protocol ID no: metoxyflurane vs. fentanyl/2018-0910-4 Version date 08-04-2019

EudraCT no: 2018-003939-30

***I hereby declare that I will conduct the study in compliance with the Protocol, ICH GCP and the applicable regulatory requirements:***

| Name | Title | Role | Signature | Date |
|---|---|---|---|---|
| Harald Lenz | MD, PhD | Principal Investigator | | |
| Kristin Sem Thagaard | MD | Sponsor's representative | | |
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# PROTOCOL SYNOPSIS

Protocol title:
Determination of analgesic equipotent doses of inhaled metoxyflurane vs. intravenous fentanyl using cold pressor test (CPT) in volunteers: A randomized, double blind, placebo-controlled crossover study.

| | |
|---|---|
| Sponsor | Kristin Sem Thagaard, Oslo University Hospital |
| Phase and study type | Phase IV, interventional. |
| Investigational Medical Product (IMP) (including active comparator and placebo) : | Penthrox 3 ml®/N02B G09/Inhalation vapour, liquid<br>Fentanyl 0.025 mg/N01A H01/Concentrate and solvent for solution for injection<br>Fentanyl 0.05 mg/N01A H01/Concentrate and solvent for solution for injection<br>Placebo: NaCl 9 mg/ml (sodium chloride) Concentrate for solution for injection and inhalation |
| Centers: | Oslo University Hospital, Oslo, Norway. |
| Study Period: | Estimated date of first patient enrolled: 01.03.19<br>Anticipated recruitment period: 1 year and 10 months<br>Estimated date of last patient (volunteer) completed: 31.12.2020<br>End of study (last visit of volunteer): 31.12.2020 |
| Treatment Duration: | Expected treatment duration pr. Patient: 2 hours x 4 treatments = 8 hours |
| Follow-up: | Expected follow-up period pr. Patient: Each treatment duration is 2 hours. No further follow-up visits. |
| Objectives | The aim of this study is to determinate equipotent doses of inhaled metoxyflurane vs. intravenous fentanyl. |
| Endpoints: | Primary endpoint: NRS (numeric rating scale, 0-10) scores during CPT 5 minutes after drug administration.<br>Secondary endpoint: NRS scores during CPT 20 minutes after drug administration. |
| Study Design: | A randomized, double blind, placebo-controlled crossover study. |
| Main Inclusion Criteria: | The volunteers should be in good health and not have any chronic illness |
| Main Exclusion Criteria | No use of pain medication and complementary medicine the last 2 days before a session. Previous substance abuse, pregnancy and known allergies or serious side effects to opioids or metoxyflurane |

| | |
|---|---|
| Sample Size: | 12 volunteers. |
| Efficacy Assessments: | Numeric rating scale (NRS) for pain, from 0 to 10. 0 = no pain to 10 = worst pain imaginable. |
| Safety Assessments: | Pulsoxymetry, end tidal CO2 and ECG will be continuously monitored during the study. Necessary acute medical equipment is available (Lærdalsbag, suction, intravenous liquid, naloxone. In addition anesthetic drugs: adrenalin, atropine and ephedrine). Respiration frequency and non-invasive blood pressure will be recorded every 5. min |
| Other Assessments: | Not applicable. |

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**LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS**

| Abbreviation or special term | Explanation |
|---|---|
| AE | Adverse Event |
| CRF | Case Report Form (electronic/paper) |
| CSA | Clinical Study Agreement |
| CTC | Common Toxicity Criteria (for cancer trials only) |
| CTCAE | Common Terminology Criteria for Adverse Event (for cancer trials only) |
| DAE | Discontinuation due to Adverse Event |
| EC | Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC) |
| GCP | Good Clinical Practice |
| IB | Investigator's Brochure |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonization |
| IMP | Investigational Medicinal Product (includes active comparator and placebo) |
| SAE | Serious Adverse Event |
| SOP | Standard Operating Procedure |
| ECG | Electrocardiogram |
| NRS | Numeric rating scale (0-10) |
| CPT | Cold pressor test |
| SpO2 | Oxygen saturation |
| REK | Regional Committees for Medical and Health Research Ethics |
| IV | intravenous |
| ETCO2 | End-tidal carbon dioxide |

# 1 INTRODUCTION

## 1.1 Background

Traumatized patients frequently experience pain prehospital due to the fear of adverse cardiovascular effects (e.g. hypotension) and respiration depression of opioid treatment, leading to insufficient analgesia.(1,2) Therefore, there is of interest to investigate other analgesics that do not have these adverse effects.

In Norway, methoxyflurane has been approved for the emergency relief of moderate to severe trauma pain in conscious adult patients. Metoxyflurane (Penthrox®) do not have these adverse effects (hypotension and respiration depression). It is easy to administrate via an inhalator, and is therefore suitable for use prehospital. This would possible help to treat pain better prehospital.

There exists no data of how effective metoxyflurane is as an analgesic compared to an opioid. The aim of this study is to determinate the equipotent doses of inhaled metoxyflurane vs. intravenous fentanyl.

## 1.2 Pre-Clinical & Clinical Experience with Investigational Medicinal Product (IMP)

Methoxyflurane (Penthrox® - inhalation vapour, liquid – C3H4Cl2F2O, ATC code: N02B G09) is a halogenated ether first used clinically as a volatile inhalational anesthetic when introduced in the 1960s.(3) Gradually the use of methoxyflurane as an anesthetic agent declined because of serious dose-related nephrotoxicity.(4) There have also been reports of hepatic failure or hepatitis. Therefore, methoxyflurane is contraindicated in patients with clinically renal impairment, and should be used with care in patients with hepatic dysfunction. There are no reports of renal toxicity in the literature at the current dose recommendation of 3 ml, repeated once with a maximum of 15 ml/week.(5-7) It has been calculated that an adult dose of 20-24 g metoxyflurane is associated with subclinical nephrotoxicity (6.0 ml delivers < 1.5 g).(8) Methoxyflurane also demonstrated an analgesic effect.(4) In the past 30 years methoxyflurane has been used as an analgesic in Australia and New Zealand. The drug has mostly been used in the emergency department and in a prehospital setting in conscious patients.(5) It is easy to administrate and has a fast onset of pain relief, approximately 5 min.(9,10)

One randomized, double-blind, placebo-controlled study of the efficacy and safety of methoxyflurane for the treatment of acute pain has been conducted.(11,12) Minor trauma patients were randomized in a 1:1 ratio to receive methoxyflurane (up to 6 ml) or placebo (normal saline), both via a Penthrox inhaler. Methoxyflurane was well tolerated. It was superior to placebo with respect to analgesic effect. No serious adverse effects where observed like e.g. hypotension or respiratory problems compared to placebo. The patients were not hypovolemic.

The opioid fentanyl (Fentanyl® - intravenous, liquid - C22H28N2O. ACT: N01A H01) is used as standard therapeutic treatment for acute pain and acute operative pain. Fentanyl is a pure opioid receptor agonist with central and peripheral effects.

## 1.3 Rationale for the Study and Purpose

Traumatized patients frequently experience pain prehospital due to the fear of adverse cardiovascular effects (e.g. hypotension) and respiration depression of opioid treatment, leading to insufficient analgesia.(1,2) Therefore, there is of interest to investigate other analgesics that do not have these adverse effects.

In Norway, methoxyflurane has been approved for the emergency relief of moderate to severe trauma pain in conscious adult patients. Metoxyflurane (Penthrox®) do not have these adverse effects (hypotension and respiration depression). It is easy to administrate via an inhalator, and is therefore suitable for use prehospital. This would possible help to treat pain better prehospital.

There exists no data of how effective metoxyflurane is as an analgesic compared to an opioid. The aim of this study is to determinate the equipotent doses of inhaled metoxyflurane vs. intravenous fentanyl.

Twelve healthy volunteers (18 – 64 years) will be enrolled in a randomized, double blind, placebo-controlled, crossover study using a standard experimental pain model: CPT- Cold pressor test (ice water). Our group has used this experimental pain model in earlier studies and a crossover study is suitable to compare different drugs.(13,14)

Possible side effects will be recorded for both metoxyflurane and fentanyl: sedation, dizziness, itching, nausea and vomiting. Respiration frequency and non-invasive blood pressure will be recorded every as possible low blood pressure or respiration depression can occur.

The aim of this study is to determinate equipotent doses of inhaled metoxyflurane vs. intravenous fentanyl. We have chosen to compare with fentanyl (the comparator) because it is a well-known drug in clinical practice for acute pain treatment. In addition, both drugs have a fast onset (minutes) and the analgesic effect last for approximately the same time interval (20-30 min). Therefore, they are comparable in a clinical setting.

There exists no exact data of equipotent doses between metoxyflurane and fentanyl, only retrospective clinical data. One retrospective study compared intranasal fentanyl with inhaled metoxyflurane for visceral pain prehospital in 1024 patients.(10) The initial dose of fentanyl was 0.018 mg and the total mean dose at hospital arrival was 0.036 mg. In the metoxyflurane group 51.9% received 3 ml, a second dose was used in 41.9% and 6.2% received a third dose. Metoxyflurane produced the greatest initial pain scores reduction, and intranasal fentanyl provided greater pain reduction by hospital arrival.

From these data we have chosen two doses of fentanyl to be compared with 3 ml Penthrox: 0.025 mg and 0.05 mg intravenous. Both drugs will also be compared to placebo (NaCl 9 mg/ml).

# 2 STUDY OBJECTIVES AND RELATED ENDPOINTS

The aim of this study is to determinate equipotent doses of inhaled metoxyflurane vs. intravenous fentanyl. We have chosen to compare with fentanyl because it is a well-known drug in clinical practice. In addition, both drugs have a fast onset (minutes) and the analgesic effect last for approximately the same time interval (20-30 min). Therefore, they are comparable in a clinical setting.

**2.1** **Primary Endpoint** NRS (numeric rating scale) scores during CPT 5 minutes after drug administration.

**2.2** **Secondary Endpoints** NRS scores during CPT 20 minutes after drug administration (15 min after last CPT).

The table below represent the study's timeline:

| Time (min) | - 15 | -10 | -5 | 0 | 5 | 10 | 15 |
|---|---|---|---|---|---|---|---|
| Control (C) | CPT | placebo (NaCl) i.v.<br>placebo (NaCl) inhal; continuous | | CPT | | | CPT |
| Fentanyl (F1) | CPT | F1 0.025 mg i.v.<br>placebo (NaCl) inhal; continuous | | CPT | | | CPT |
| Fentanyl (F2) | CPT | F2 0.05 mg i.v.<br>placebo (NaCl) inhal; continuous | | CPT | | | CPT |
| Metoxyflurane (M) | CPT | placebo (NaCl) i.v.<br>M 3 ml inhal; continuous | | CPT | | | CPT |

# 3 OVERALL STUDY DESIGN

The study is a phase 4

This is a randomized, double blind, placebo-controlled crossover study in volunteers

| | |
|---|---|
| Study Period | Estimated date of first patient enrolled: 01.03.2019<br>Anticipated recruitment period: 22 months<br>Estimated date of last patient completed:31.12.2020 |
| Treatment Duration: | 2 h x 4. Totally 8 hours |
| Follow-up: | No further follow-up after the four sessions. |

# 4 STUDY POPULATION

## 4.1 Selection of Study Population

The study will be conducted at Oslo University Hospital in Oslo, Norway. Only healthy volunteers will be included (see inclusion/exclusion criteria).

## 4.2 Number of Patients

12 volunteers will be recruited.

## 4.3 Inclusion Criteria

1. Healthy volunteers
2. Age 18 – 64
3. Both sex
4. No chronic disease
5. No regular medication
6. Recruited from the general population
7. Signed informed consent and expected cooperation of the subjects for the treatment and follow up must be obtained and documented according to ICH GCP, and national/local regulations

## 4.4 Exclusion Criteria

1. Use of pain medication the last 2 days before a session
2. Use of complementary medicine the last 2 days before a session
3. Use of regular medication
4. Previous substance abuse
5. Pregnancy
6. Know allergies or serious side effects to opioids or metoxyflurane
7. Use of alcohol last 24 h before each session

8. **Exclusion criteria with respect to fentanyl:**
9. Hypersensitivity opposite the active substance (fentanyl) or other opioids
10. Hypersensitivity opposite the excipients (to fentanyl): sodiumclorid, water for injection, hydrochloric acid or sodium hydroxide
11. Respiratory depression without artificial ventilation

12. Use of MAO-inhibitor or use of MAO-inhibitor by two weeks before inclusion
13. Elevated intracranial pressure or brain trauma
14. Hypovolemia or hypotension
15. Myasthenia gravis

16. **Exclusion criteria with respect to metoxyflurane:**
17. Use metoxyflurane as anesthetic
18. Hypersensitivity opposite metoxyflurane or fluorinated anesthetics
19. Hypersensitivity opposite the excipient (to metoxyflurane): Butylhydroksytoluen
20. Malignant hyperthermia or persons with suspect genetic predisposition for malignant hyperthermia
21. History (to the volunteer or family) of serious adverse effects after administration of inhalation anesthetics
22. Volunteers showing sign of liver damage after use of metoxyflurane or halogenated anesthetics
23. History of liver disease
24. Clinical significant reduced kidney function or history of kidney disease
25. Changed of level of consciousness of any cause, including brain trauma, drugs or alcohol
26. Clinical detected cardiovascular unstability
27. Clinical detected respiratory depression

# 5 TREATMENT

For this study Penthrox® (methoxyflurane) 3 ml / N02B G09 /Inhalation vapour, liquid, and the active comparator Fentanyl® / N01A H01 / Concentrate and solvent for solution for injection and intravenous use (with 2 different doses 0,025 mg and 0,05 mg) are defined as Investigational Medicinal Products (IMP). The dosages used for both metoxyflurane and fentanyl in this study are according to approved indications as described in the SPC for both drugs. NaCl 9 mg/ml (sodium chloride -saline) concentrate and solvent for solution for intravenous and inhalation use is also defined as IMP. NaCl 9 mg/ml will be used as placebo.

## 5.1 Drug Identity, Supply and Storage

Penthrox® (methoxyflurane), 3 ml / ATC-nr. N02B G09 / Inhalation vapour, liquid. For inhalation use. (Mundiphrama).

Fentanyl® 2 ml, 0.05 mg/ml / ATC-nr. N01A H01 / Concentrate and solvent for solution for injection and intravenous use (Hameln).

Natriumklorid 9 mg/ml, 10 ml amp. / ATC-nr: B05BB01 / Concentrate and solvent for solution for injection and intravenous use (Braun). - placebo

Natriumklorid 9 mg/ml, 10 ml amp. / ATC-nr: B05BB01 / Concentrate and solvent for inhalation (Braun).- placebo.

All three drugs can be stored in room temperature. The drugs will be in a dark, locked storage room for medicines in Research nurse Tomas Draegni's office at the Department of Research and Development, Division of Emergencies and Critical Care, Oslo University Hospital. Tomas Draegni will assist Harald Lenz in the study..

## 5.2 Dosage and Drug Administration

A nurse, not participating in the study, will prepare the drugs for use at each session.

1) Fentanyl 0.025 mg (0.5 ml) diluted with natriumklorid 9 mg/ml (1.5 ml), in a 2 ml syringe for intravenous use

2) Fentanyl 0.05 mg (1.0 ml) diluted with natriumklorid 9 mg/ml (1.0 ml), in a 2 ml syringe for intravenous use

3) Natriumklorid 9 mg/ml (2.0 ml) in a 2 ml syringe for intravenous use

4) Penthrox® Inhalator (methoxyflurane) 3 ml, Inhalation vapour

5) Penthrox® Inhalator (natriumklorid) 3 ml, Inhalation vapour

Timing of administration of drugs se 2.2 secondary endpoints, study's timeline.

The study medicines will be administered to the subject by authorized site personnel only (Harald Lenz and Tomas Drægni).

## 5.3 Duration of Therapy

Every subject will receive 4 different treatments in a randomized sequence with an interval of at least 3 days between each session. Each session lasts for 2 hours. The actually time-line for the study is 30 min. The preparation before start will take 30 min. Then one hour of recovery before end of each session. Both drugs, metoxyflurane and fentanyl, will at that time be eliminated from the body.

## 5.4 Premedication and Monitoring

No premedication will be used.
Vital sign assessment (blood pressure and respiration frequency) will be registered during each session.
Continuous ECG, heart rate, ETCO2 and SpO2 measurement will be registered throughout each session.

## 5.5 Schedule Modifications

No dose modifications are allowed.

## 5.6 Concomitant Medication

No use of pain medication and complementary medicine the last 2 days before a session. No concomitant drugs are allowed to take.
Prohibited medication:

- Hypersensitivity opposite the active substance (fentanyl) or other opioids.
- Hypersensitivity opposite metoxyflurane, fluorinated anesthetics or butylhydroksytoluen
- MAO-inhibitor or use of MAO-inhibitor by two weeks before inclusion.

If any adverse effects we have rescue medications: naloxone (adverse effects to opioids), adrenalin (low blood pressure, anaphylaxis), atropine (low pulse) and ephedrine (low blood pressure and/or low pulse)

## 5.7 Subject Compliance

The study medicines will be administered to the subject by authorized site personnel only.

## 5.8 Drug Accountability

The responsible site personnel will confirm receipt of study drug and will use the study drug only within the framework of this clinical study and in accordance with this protocol. Receipt, distribution, return, and destruction (if any) of the study drug must be properly documented according to the sponsor's agreed and specified procedures.

The drugs will be stored according to Oslo University Hospital guidelines for narcotics before distribution (locked storage room for medicines). The drugs will be treated by a nurse not participating in the study. Any remaining study medicine will be logged in the CRF by the nurse before being disposed of according to hospital standards.

## 5.9 Drug Labeling

The investigational product will have a label permanently affixed to the outside and will be labeled according with ICH GCP and national regulations, stating that the material is for clinical trial / investigational use only and should be kept out of reach of children.

Labeling of the IMPs will be done by one a nurse anesthetist not participating in the study. The study drugs, will be distributed in a pre-packed in identical, opaque envelopes (the same day as the drugs will be used). The envelopes are not to be broken until randomization of the patient is done

The labeling will be in Norwegian. One label is attached to the syringe with the most critical information: organizer serial number; "Til klinisk utprøving"; Oppbevares utilgjengelig for barn; See pictures:

Labels will also include blank lines (in Norwegian) for:

- Patient's initials
- Patient's enrolment code
- Protocol code
- Date dispensed
- Name of prescribing doctor
- Name of Principal Investigator

## 5.10 Subject Numbering

Each subject is identified in the study by a unique subject number that is assigned when subject signs the Informed Consent Form. Once assigned the subject number cannot be reused for any other subject. A record in the clinical study file will keep track of the next number to assign. Once assigned the subject number cannot be reused for any other subject.

# 6 STUDY PROCEDURES

## 6.1 Flow Chart

Screening period within 1-14 days of treatment. Inclusion/exclusion evaluation. A medical history will be performed.

Three pilots will be performed before the study start to investigate whether the two selected doses are representative to compare with the 3 ml metoxyflurane dose. If the pilots demonstrate large differences in the CPT scores at time zero between the selected fentanyl doses and metoxyflurane, a change in the protocol has to be performed. This will of lead to an application to REK about the changes (and the Norwegian Medicines Agency).

Flow chart:

| Time (min) | - 15 | -10 | -5 | 0 | 5 | 10 | 15 |
|---|---|---|---|---|---|---|---|
| Control (C) | CPT | | placebo (NaCl) i.v.<br>placebo (NaCl) inhal; continuous | CPT | | | CPT |
| Fentanyl (F1) | CPT | | F1 0.025 mg i.v.<br>placebo (NaCl) inhal; continuous | CPT | | | CPT |
| Fentanyl (F2) | CPT | | F2 0.05 mg i.v.<br>placebo (NaCl) inhal; continuous | CPT | | | CPT |
| Metoxyflurane (M) | CPT | | placebo (NaCl) i.v.<br>M 3 ml inhal; continuous | CPT | | | CPT |

Abbrevations: NaCl: natriumcloride, i.v: intravenously, inhal: inhalation, CPT: Cold pressor test.

Each session starts with a CPT (time -15 minutes). Then a 10 minutes rest before the subject receives a syringe of either NaCl or a dose of fentanyl intravenously (time -5 min). At the same time the subject begin to inhale either metoxyflurane or NaCl through the inhalator. The subject should first take 10 breath through the inhalator. This will take approximately 1-1.5 minutes. The subject then take a break, and then inhale the rest of the dosage before time zero.

At time zero a new CPT will be performed. At time 15 min the last CPT will be performed.

The subjects will undergo CPT (cold pressor test) to determine the analgesic effect of the drugs.(13,14) The CPT will be conducted using a temperature-controlled bath with circulating 3°C water (FP 45-HE Refrigerated/Heating Circulator,

Julabo Labortechnic, 77960 Seelback, Germany). The subjects submerge their right hand to the wrist with fingers abducted for up to 90 s. The endpoints are NRS scores every 10 s.This test will be performed 3 times for each session.

The actual implementation of the study will take 30 minutes. We estimate 30 minutes of preparation and 1 hour of observation after the execution of the protocol. Totally, each session will last for 2 hours.

A cannula will be placed on the subject left hand back. The right hand will be submerge into the ice water.

Pulsoxymetry, ETCO2 and ECG will be continuously monitored during the study. Necessary acute medical equipment is available (Lærdalsbag, suction, intravenous liquid, naloxone. In addition anesthetic drugs: adrenalin, atropine and ephedrine).

Side effects will be recorded: sedation, dizziness, itching, nausea and vomiting. Respiration frequency and non-invasive blood pressure will be recorded every 5. min

## 6.2 By Visit

**Informed consent**

Informed consent must have been given voluntarily by each subject before the study specific procedures are initiated. A medical history will be performed.

**Clinical status**

Weight, height, blood pressure, pulse, ECG, ETCO2 and SpO2 will be performed before each session

**Concomitant medication**

All concomitant medication (incl. vitamins, herbal preparation and other "over-the-counter" drugs) used by the subject within 28 days of treatment start will be recorded in the CRF.

### 6.2.1 Before Treatment Starts

- Evaluating patient eligibility: The subjects should be in good health and not have any chronic illness. Both sex will be included. The subject will be recruited from the general population.
- Assessing baseline values of parameters used as end-points: Each session starts with a CPT (time -15 minutes), see flow-chart 6.1.The NRS values from the first CPT are the baseline values the end-points will be evaluated from in each session.

### 6.2.2 During Treatment

Each session starts with a CPT (time -15 minutes). Then a 10 minutes rest before the subject receives a syringe of either NaCl or a dose of fentanyl intravenously (time -5 min). At the same time the subject begin to inhale either metoxyflurane or NaCl through the inhalator. The subject should first take 10 breath through the inhalator. This will take approximately 1-1.5 minutes. The subject then take a break, and then inhale the rest of the dosage before time zero.

At time zero a new CPT will be performed. At time 15 min the last CPT will be performed.

The subjects will undergo CPT (cold pressor test) to determine the analgesic effect of the drugs.(13,14) The CPT will be conducted using a temperature-controlled bath with circulating 3°C water (FP 45-HE Refrigerated/Heating Circulator, Julabo Labortechnic, 77960 Seelback, Germany). The subjects submerge their right hand to the wrist with fingers abducted for up to 90 s. The endpoints are NRS scores every 10 s.This test will be performed 3 times for each session.

### 6.2.3 End of Treatment and/or End of Study Visit

The actual implementation of the study will take 30 minutes. We estimate 30 minutes of preparation and 1 hour of observation after the execution of the protocol. Totally, each session will last for 2 hours.

### 6.2.4 Withdrawal Visit

If one participant experience very unpleasant or a severe adverse effect during a session, the session will be terminated. The participant will then be excluded from the rest of the study.

### 6.2.5 After End of Treatment (Follow-up)

After ending the last of 4 sessions, there will be no further follow-up

## 6.3 Criteria for Patient Discontinuation

Subjects may be discontinued from study treatment and assessments at any time. Specific reasons for discontinuing a subject for this study are:

- Voluntary discontinuation by the patient who is at any time free to discontinue his/her participation in the study, without prejudice to further treatment.
- Safety reason as judged by the Principal Investigator
- Major protocol deviation
- Incorrect enrolment i.e., the patient does not meet the required inclusion/exclusion criteria for the study
- Patient lost to follow-up
- A female patient becoming pregnant
- Deterioration in the patient's condition which in the opinion of the Principal Investigator warrants study medication discontinuation (to be records as an AE or under Investigator Discretion)
- Patient's non-compliance to study treatment and/or procedures
- Serious adverse effects of any of the drugs

## 6.4 Procedures for Discontinuation

### 6.4.1 Patient Discontinuation

Subject who gets any kind of severe adverse effects will be followed up.

All patients randomized will be included in the study population.

Patients who withdraw or are withdrawn from the study after randomisation cannot be replaced.

### 6.4.2 Trial Discontinuation

The whole trial may be discontinued at the discretion of the PI or the sponsor in the event of any of the following:

- Occurrence of AEs unknown to date in respect of their nature, severity and duration
- Medical or ethical reasons affecting the continued performance of the trial
- Difficulties in the recruitment of patients
- Cancellation of drug development

The sponsor and principal investigator(s) will inform all investigators, the relevant Competent Authorities and Ethics Committees of the termination of the trial along with the reasons for such action. If the study is terminated early on grounds of safety, the Competent Authorities and Ethics Committees will be informed within 15 days.

## 6.5 Laboratory Tests

No laboratory tests will be performed.

# 7 ASSESSMENTS

## 7.1 Assessment of Response

The following parameters of response will be recorded:

Pain scores (NRS):

The subjects will undergo CPT (cold pressor test) to determine the analgesic effect of the drugs.(13,14) The CPT will be conducted using a temperature-controlled bath with circulating 3°C water (FP 45-HE Refrigerated/Heating Circulator, Julabo Labortechnic, 77960 Seelback, Germany). The subjects submerge their right hand to the wrist with fingers abducted for up to 90 s. The endpoints are NRS scores every 10 s.This test will be performed 3 times for each session.

## 7.2 Safety and Tolerability Assessments

Safety will be monitored by the assessments described below as well as the collection of AEs at every session. Significant findings that are present prior to the signing of informed consent must be included in the relevant medical history/ current medical condition page of the CRF. For details on AE collection and reporting, refer to Section 8.

Pulsoxymetry, ETCO2 and ECG will be continuously monitored during the study. Necessary acute medical equipment is available (Lærdalsbag, suction, intravenous liquid, naloxone. In addition anesthetic drugs: adrenalin, atropine and ephedrine).

Side effects will be recorded: sedation, dizziness, itching, nausea and vomiting. Respiration frequency and non-invasive blood pressure will be recorded every 5. min

## 7.3 Other Assessments

Summary of benefit-risk to the volunteers in this study:

There are no special benefits to the volunteers to participate in this study.

It is important to record a detailed anamnesis before inclusion. Especially with respect to exclusion criteria mention in chapter 4.4

It is a certain risk that the participant may experience a feeling of «high» or drugged when he/she gets fentanyl intravenously. Therefore, previously drug-addicted will not be included in the study. The dosages of fentanyl are small

and the participants will be exposed repetitive times to the ice water test (cold pressor test - CPT). The CPT is considerable painful and a possibly feeling of “high” will disappear when the pain increase.

The participant will be informed about the painful ice-water test. The CPT is harmless, but participants that experience the pain as unbearable the experiment will be stopped.

Metoxyflurane may be nephrotoxic in anesthetic doses. 6 ml metoxyflurane is equivalent with 1.5 g. Nephrotoxic dose has been estimated to be approximately 20-24 g. (8). There are no published studies on cases of kidney failure with dosages of 3-6 ml. In our study, the participants receive only 3 ml once. Persons with any kind of history of kidney disease will not be included.

Common side effects like sedation, nausea, vomiting, dizziness, itching and respiration depression (especially to fentanyl) will be continuously monitored during the study. If some of the side effects become too bothersome to the participant, the experiment will be stopped.

Necessary acute medical equipment is available (Lærdalsbag, suction, naloxone, adrenaline, atropine and ephedrine) will be kept nearby.

Vital sign assessment (blood pressure and respiration frequency) will be registered every 5. min during each session. Continuous ECG, heart rate, ETCO2 and SpO2 measurement will be registered throughout each session. This close monitoring will help us in detecting severe adverse effects like malignant hyperthermia (elevated ETCO2), anaphylactoid or anaphylactic reactions. The participants have intravenous access, and the i.v. access can of course be used in a setting of anaphylactoid or anaphylactic reactions.

All adverse events and serious adverse events will be reported as defined in section 8.1.1 will be recorded in the patient's CRF.

# 8 SAFETY MONITORING AND REPORTING

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an adverse event (AE) or serious adverse event (SAE). Each patient will be instructed to contact the investigator immediately should they manifest any signs or symptoms they perceive as serious.

The methods for collection of safety data are described below.

## 8.1 Definitions

### 8.1.1 Adverse Event (AE)

An AE is any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

The term AE is used to include both serious and non-serious AEs.

AE that do not need to be recorded (expected AE): for opioid (fentanyl): sedation, dizziness, itching, nausea and vomiting are frequent AE’s. If the AE’s are mild and/or acceptable for the subject, the subject will not be excluded from the study and the AE do not need to be recorded. Mild respiration depression (resp frequency > 8/min) will be accepted as AE that do not need to be recorded.

If an abnormal laboratory value/vital sign are associated with clinical signs and symptoms, the sign/symptom should be reported as an AE and the associated laboratory result/vital sign should be considered additional information that must be collected on the relevant CRF.

### 8.1.2 Serious Adverse Event (SAE)

Any untoward medical occurrence that at any dose:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

Examples of possible SAE in our study:

- Respiratory depression which may be life-threatening and/or require prolonged hospitalization and/or result in persistent disability.
- Cardiovascular collapse secondary to respiratory depression or due to anaphylactic reactions or vasodilatation by other mechanisms.
- Anaphylactoid or anaphylactic reactions.

Medical and scientific judgment is to be exercised in deciding on the seriousness of a case. Important medical events may not be immediately life threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent one of the listed outcomes in the definitions above. In such situations, or in doubtful cases, the case should be considered as serious. Hospitalization for administrative reason (for observation or social reasons) is allowed at the investigator's discretion and will not qualify as serious unless there is an associated adverse event warranting hospitalization.

### 8.1.3 Suspected Unexpected Serious Adverse Reaction (SUSAR)

Suspected Unexpected Serious Adverse Reaction: SAE (see section 8.1.2) that is unexpected as defined in section 8.2 and possibly related to the investigational medicinal product(s)..

This protocol has included a range of symptoms and vital signs, which are well-known side-effects/adverse events to all opioids, including the study medicines. Any such event mentioned in the protocol will be considered as SAE. Any event other than those mentioned in the SmPCs of the study medicines may be classified as SUSAR.

## 8.2 Expected Adverse Events

The following side-effects/adverse events: respiratory depression, sedation, nausea, vomiting, pruritus, dizziness and headache will be registered in the CRF.

Such AEs will be registered in the AE/SAE section of the CRF. Further adverse events listed in the SmPCs for the study drugs will also be registered as AE/SAE if they occur

1) Penthrox® 3 ml / ATC-nr. N02B G09/ Inhalation vapour, Mundiphrama, Norwegian version section 4 "Bivirkninger".

2) Fentanyl® 2 ml, 0.05 mg/ml /ATC-nr. N01A H01/ intravenous use,Hameln, Norwegian version section 4 "Bivirkninger".

## 8.3 Time Period for Reporting AE and SAE

For each subject the standard time period for collecting and recording AE and SAEs will begin at start of study medicine and will continue until end of treatment as defined in paragraph 5.3.

For each patient the standard time period for collecting and recording AE and SAEs will begin at first session of four sessions and will continue for at least 1 h following the last dose of study treatment for each subject.

During the course of the study all AEs and SAEs will be proactively followed up for each subject; events should be followed up to resolution. Every effort should be made to obtain a resolution for all events, even if the events continue after discontinuation/study completion.

## 8.4 Recording of Adverse Events

If the patient has experienced adverse event(s), the investigator will record the following information in the CRF:

- The nature of the event(s) will be described by the investigator in precise standard medical terminology (i.e. not necessarily the exact words used by the patient).
- The duration of the event will be described in terms of event onset date and event ended data.
- The intensity of the adverse event: define as applicable the criteria used.
- The Causal relationship of the event to the study medication will be assessed as one of the following (the definitions below are according to WHO but can be deviated from if other/fewer categories are more suitable for the study):

  **Unrelated:**

  There is not a temporal relationship to investigational product administration (too early, or late, or investigational product not taken), or there is a reasonable causal relationship between non-investigational product, concurrent disease, or circumstance and the AE.

  **Unlikely:**

  There is a temporal relationship to investigational product administration, but there is not a reasonable causal relationship between the investigational product and the AE.

  **Possible:**

  There is reasonable causal relationship between the investigational product and the AE. Dechallenge information is lacking or unclear.

  **Probable:**

  There is a reasonable causal relationship between the investigational product and the AE. The event responds to dechallenge. Rechallenge is not required**.**

**Definite:**

There is a reasonable causal relationship between the investigational product and the AE.

- Action taken
- The outcome of the adverse event – whether the event is resolved or still ongoing.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 8.1. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but is not an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke, but would be an SAE.

## 8.5 Reporting Procedure

### 8.5.1 AEs and SAEs

All adverse events and serious adverse events that should be reported as defined in section 8.1.1 will be recorded in the patient's CRF.

SAEs must be reported within 24 hours after the site has gained knowledge of the SAE. Every SAE must be documented by the investigator on the SAE pages (to be found in the investigator site file). The investigator site file is as part of the CRF. The Serious Adverse Event Report Form must be completed, signed and sent to sponsor. The initial report shall promptly be followed by detailed, written reports if necessary. The initial and follow-up reports shall identify the trial subjects by unique code numbers assigned to the latter.

The sponsor keeps detailed records of all SAEs reported by the investigators and performs an evaluation with respect to causality and expectedness. Based on, among other, SAE reports the sponsor will evaluate whether the risk/benefit ratio associated with study is changed.

### 8.5.2 SUSARs

SUSARs will be reported to the Competent Authority (The Norwegian Medicines Agency and REK sør-øst C) according to national regulation. The following timelines should be followed:

The sponsor will ensure that all relevant information about suspected serious unexpected adverse reactions that are fatal or life-threatening is recorded and reported as soon as possible to the Competent Authority in any case no later than seven (7) days after knowledge by the sponsor of such a case, and that relevant follow-up information is subsequently communicated within an additional eight (8) days.

All other suspected serious unexpected adverse reactions will be reported to the Competent Authority concerned as soon as possible but within a maximum of fifteen (15) days of first knowledge by the sponsor.

SUSARs will be reported to The Norwegian Medicines Agency (post@legemiddelverket.no) using the CIOMS form no later than 7 days after the incident.

Sponsor will also report SUSAR to the EMEAs EudraVigilance database. This may be done with assistance from Hameln or Mundipharma.

### 8.5.3 Annual Safety Report

Once a year throughout the clinical trial, the sponsor will provide the Competent Authority with an annual safety report. The format will comply with national requirements.

### 8.5.4 Clinical Study Report

The adverse events and serious adverse events occurring during the study will be discussed in the safety evaluation part of the Clinical Study Report.

## 8.6 Procedures in Case of Emergency

The investigator is responsible for assuring that there are procedures and expertise available to cope with emergencies during the study.

- The randomization code will be stored in Tomas Drægni's private office, Department of Anesthesiology, Oslo University Hospital, building 7, Ullevål. For safety reasons a sealed copy of the randomization code will also be available at the place where the study will be performed. This will be accessible 24/7. In case of an unexpected medical incident the code will be broken to ensure proper treatment. Each envelope with drugs will have a corresponding sealed envelope with the randomization code for the drug-envelope. This will enable us to identify the study medication given to one single subject without breaking the full randomization code.

- Harald Lenz (consultant anesthesiology, PhD) and Tomas Drægni (anesthesist nurse) will be responsible for the implementation of the data. They are well trained in handling of patients with respiratory depression or other type of emergencies as part of professional training and practice.

Interventions if SpO2 < 90% for more than 3 minutes or immediately if SpO2 < 85% or respiratory rate < 8:

1) Stimulate patient to achieve respiratory rate > 8 and/or deeper respiratory action.

2) Supplemental oxygen to 2 l/min.

3) Reversal agent: Naloxone® (naloxone) 0.1 mg IV. Repeated every 2-5 minutes until response.

4) Bag-mask ventilation and consider other reasons for hypoxemia than opioid effect.

## 8.7 Data Monitoring Committee (DMC)

The investigator will be visited on a regular basis by the Clinical Study Monitor (Department of Clinical Research Support at Oslo University Hospital)

# 9 DATA MANAGEMENT AND MONITORING

## 9.1 Case Report Forms

### For Electronic Case Report Forms (eCRFs) and paper Case Report Forms (pCRF)

The CRF for this study will be designed and produced by research nurse Tomas Drægni and principal investigator Harald Lenz, Oslo University Hospital.

The designated investigator staff will enter the data required by the protocol into the paper Case Report Forms (pCRF/CRF). The Investigator is responsible for assuring that data entered into the CRF is complete, accurate, and that entry is performed in a timely manner. The signature of the investigator will attest the accuracy of the data on each CRF. If any assessments are omitted, the reason for such omissions will be noted on the pCRFs. Corrections, with the reason for the corrections will also be recorded.

The data will be entered into a database and double-checked for erroneous entries. The setup of the database system will be performed by research nurse Tomas Drægni, Oslo University Hospital, Ullevål. Oslo University Hospital has a safe database (K. sensitive) were the data will be saved.

After database lock, the investigator will receive a digital copy of the subject data for archiving at the investigational site.

## 9.2 Source Data

Source data are all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

The records for each subject should contain information, which is important for the subject's safety and to fulfill the requirement that critical study data should be verifiable

Specify and provide details if any source data will be recorded directly into the Case Report Form (meaning that for the defined parameters, CRF is source data and not the hospital records).

A source data list will be agreed upon for each site specifying the source at a module or a variable level.

## 9.3 Study Monitoring

The investigator will be visited on a regular basis by the Clinical Study Monitor (Department of Clinical Research Support at Oslo University Hospital), who will check the following:

- Informed consent process
- Reporting of adverse events and all other safety data
- Adherence to protocol
- Maintenance of required regulatory documents
- Study Supply accountability
- Facilities and equipments (example: laboratory, pharmacy, ECG machine, etc…) if applicable
- Data completion on the CRFs including source data verification (SDV).

The monitor will review the relevant CRFs for accuracy and completeness and will ask the site staff to adjust any discrepancies as required.

Sponsor's representatives (e.g. monitors, auditors) and/or competent authorities will be allowed access to source data for source data verification in which case a review of those parts of the hospital records relevant to the study will be required.

## 9.4 Confidentiality

The investigator shall arrange for the secure retention of the patient identification and the code list. Patient files shall be kept for the maximum period of time permitted by each hospital. The study documentation (CRFs, Site File etc) shall be retained and stored during the study and for 15 years after study closure. All information concerning the study will be stored in a safe place inaccessible to unauthorized personnel.

## 9.5 Database management

The data will be stored in a dedicated and secured area at:

- pCRF: in a locked filing cabinet in the office of research nurse Tomas Drægni at the Department of Anesthesiology, Oslo University Hospital, building 7, Ullevål.

Data will be stored in a de-identified manner, where each study participant is recognizable by his/her unique trial subject number. The code list to link pCRF to patient in case of need for identifying data will be stored in a locked filing cabinet in the private office of research nurse Tomas Drægni at the Department of Anesthesiology, Oslo University Hospital, building 7, Ullevål.

After transferal of data from pCRF to the database, the pCRF will be stored in in the research archive at the Department of Anesthesiology, Oslo University Hospital, building 36, Ullevål.

- The database will be stored in the designated space in the secure research server for Oslo University Hospital (Domain “Felles”-”Sensitivt”; File “Forskning03”).

The data will be stored until 31.12.2035.

Data management will be performed by research nurse Tomas Drægni and principal investigator Harald Lenz, Oslo University Hospital. The Data management procedures will be performed in accordance with the department’s SOPs and ICH guidelines.

Data entered into the database will be validated by double-checking for erroneous entries against the CRF and hospital records.

# 10 STATISTICAL METHODS AND DATA ANALYSIS

## 10.1 Determination of Sample Size

The power analysis is based on data from one of our previous study using the same model, the cold pressor test.(13)

This is a crossover study. Data on standard deviation of differences between the conditions in a paired comparison is used in the calculation. nQuery Advisor software was used to calculate the sample size and to do the power analysis” A sample size of 10 will have 80% power to detect a difference in means of 0,500 (e.g. a First condition mean, of 6,000 and a Second condition mean of 5,500), assuming a standard deviation of differences of 0,500, using a paired t-test with a 0,050 two-sided significance level . We will include 12 subjects to achieve a more exact block-randomization.

## 10.2 Randomization

### 10.2.1 Allocation- sequence generation

Key elements to specify regarding allocation of treatment are:

- Method of generating the allocation sequence: computer-generated random sequential allocation. Professor Leiv Arne Rosseland will generate the allocation sequence.

- Allocation ratio: 1:1.

- Type of randomization: blocked randomization. Details of blocked randomization are provided in a separate document that is unavailable to those who enroll subjects or assign treatment.

### 10.2.2 Allocation- procedure to randomize a subject

The study investigators will enroll the subjects. After the informed consent form is collected, the subjects will be allocated by choosing the next available treatment stored in sequentially numbered, opaque, sealed envelopes

### 10.2.3 Blinding and emergency unblinding

The investigators (Harald Lenz and Tomas Drægni) and the subject will be blinded for the randomization and the study medication. The subject may theoretically identify the study medication from drug characteristics, but we consider this unlikely.

A doctor and a nurse will pack and label the study medicine. They will not be blinded, but will not participate in the handling of the subjects.

Emergency unblinding should generally only be done if the safety and well-being of the subject is being compromised. The decision to reveal the treatment allocation during the study should be done exclusively by the principal investigator.

Un-blinding of the treatment allocation is permissible only if the safety and well-being of the subject is being compromised. The decision to reveal the treatment allocation during the study may only be done by the principal investigator. The date and time of un-blinding must be documented in the CRF and in the patient's hospital records.

In the event of an SAE, the Investigator will break the treatment code.

## 10.3 Population for Analysis

The following populations will be considered for the analyses:

- The full analysis population: All randomized subjects having received at least one dose of study medication and were a minimum of data is collected.

- The per-protocol population: All randomized subjects completing the study without major protocol violations. Definition of major protocol violations will be specified in the statistical analysis plan, and the final criteria will be defined prior to database lock. Data concerning the primary endpoint should be collected.

- Safety population: Includes all randomized subjects who have received at least one dose of study medication. Subjects who withdraw from the study will be included in the safety analysis. A list of withdrawn subjects, preferably with the reasons for withdrawal, will be made.

- The primary statistical analysis will be based on the subjects meeting the definition of the protocol population according to inclusion and exclusion criteria and with no major protocol violations.

- The secondary analysis will include all patients receiving study treatment.

## 10.4 Planned analyses

The main statistical analysis is planned when the planned number of patients have been included and have finalized data collection. Furthermore all data has to be entered, verified and validated according to the data management plan.

Prior to the main statistical analysis, the data base will be locked for further entering or altering of data. A separate statistical analysis plan (SAP) will provide further details on the planned statistical analyses. The SAP will be finalized, signed and dated prior to database lock. The treatment allocation will be revealed after the database lock and used in the statistical analysis. There will be no interim analysis.

Deviation from the original statistical plan will be described and justified in the Clinical Study Report. Amendments to plan can be done until day of DB lock.

## 10.5 Statistical Analysis

### 10.5.1 Primary analysis and Secondary analysis

The linear mixed-model procedure will be used to compare the effect of different treatments in the NRS in the cold-pressor pain model. This is a variance component model that takes into account correlations/dependence as a result of repeated treatments, carryover effects, and repeated observations in each treatment session on each subject. This statistical analysis is appropriate for a crossover study with repeated measurements.

The dependent variables were changes from baseline in the NRS in the cold-pressor pain model. For all analyses, pairwise comparisons between the treatments will be made only if the overall test for the difference between all treatments was significant at the level of 0.05. This Fisher's least significant difference method provides protection for multiple comparisons. Data will be analyzed in SPSS.

The primary endpoint is NRS during CPR at time zero

The secondary endpoint is NRS during CPR at time 15 min

Statistical hypothesis test:

- Null hypothesis: The difference in pain between the treatment (metoxyflurane) is at least 0.5 point on the 0-10 NRS scale in favor of the control treatment (fentanyl 0.05 mg).

- Alternative hypothesis: The difference in pain between the treatment (metoxyflurane) is less than 0.5 point on the 0-10 NRS scale in favor of the control treatment (fentanyl 0.025 mg).

### 10.5.2 Safety analyses

The safety analyses population will include all subjects who completed all 4 treatments.

# 11 STUDY MANAGEMENT

## 11.1 Investigator Delegation Procedure

The principal investigator is responsible for making and updating a "delegation of tasks" listing all the involved co-workers and their role in the project. He will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information of relevance to the performance of this study is forwarded to the staff involved.

## 11.2 Protocol Adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations.
All significant protocol deviations will be recorded and reported in the Clinical Study Report (CSR).

## 11.3 Study Amendments

If it is necessary for the study protocol to be amended, the amendment and/or a new version of the study protocol (Amended Protocol) must be notified to and approved by the Competent Authority and the Ethics Committee according to EU and national regulations.

## 11.4 Audit and Inspections

Authorized representatives of a Competent Authority and Ethics Committee may visit the centre to perform inspections, including source data verification. Likewise the representatives from sponsor may visit the center to perform an audit. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (ICH GCP), and any applicable regulatory requirements. The principal investigator will ensure that the inspectors and auditors will be provided with access to source data/documents.

# 12 ETHICAL AND REGULATORY REQUIREMENTS

The study will be conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice and applicable regulatory requirements. Registration of patient data will be carried out in accordance with national personal data laws.

## 12.1 Ethics Committee Approval

The study protocol, including the patient information and informed consent form to be used, must be approved by the regional ethics committee before enrolment of any patients into the study. The application deadline for REC South East will be 11.12.2018.

The investigator is responsible for informing the ethics committee of any serious and unexpected adverse events and/or major amendments to the protocol as per national requirements.

## 12.2 Other Regulatory Approvals

The protocol will be submitted and approved by the applicable competent authorities before commencement of the study:

The protocol will also be registered in www.clinicaltrials.gov and kliniskestudier.helsenorge.no before inclusion of the first subject.

Application to personvernombud at Oslo University Hospital.

## 12.3 Informed Consent Procedure

The investigator is responsible for giving the subjects full and adequate verbal and written information about the nature, purpose, possible risk and benefit of the study. They will be informed as to the strict confidentiality of their patient data, but that their medical records may be reviewed for trial purposes by authorized individuals other than their treating physician.

It will be emphasized that the participation is voluntary and that the patient is allowed to refuse further participation in the protocol whenever she/he wants. This will not prejudice the patient's subsequent care. Documented informed consent must be obtained for all subjects included in the study before they are registered in the study. This will be done in accordance with the national and local regulatory requirements. The investigator is responsible for obtaining signed informed consent.

A copy of the patient information and consent will be given to the subjects. The signed and dated patient consent forms will be filed in the Investigator Site File binder and also scanned to be part of the patient's electronic medical record at the hospital.

## 12.4 Subject Identification

The investigator is responsible for keeping a list of all subjects (who have received study treatment or undergone any study specific procedure) including patient's date of birth and personal number, full names and last known addresses.

The patients will be identified in the CRFs by patient number, initials and date of birth.

# 13 TRIAL SPONSORSHIP AND FINANCING

The study is sponsored by funds from the Department of Anesthesiology, Oslo University Hospital.

# 14 TRIAL INSURANCE

For studies conducted in Norway: Harald Lenz has insurance coverage for the participants in this study through membership of the Drug Liability Association for the appropriate numbers included each year.

# 15 PUBLICATION POLICY

Upon study completion and finalization of the study report, the results of this study will either be submitted for publication and/or posted in a publicly assessable database of clinical study results.

The results of this study will also be submitted to the Competent Authority and the Ethics Committee according to EU and national regulations.

All personnel who have contributed significantly with the planning and performance of the study (Vancouver convention 1988) may be included in the list of authors.

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