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Statistical Analysis Plan (SAP)

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1.0 INTRODUCTION

Adequate uterus contraction after delivery of the baby is necessary to avoid excessive bleeding. Prophylactic administration of an oxytocin receptor agonist is first line practice. Intravenous injection of oxytocin has been the standard procedure, but serious cardiovascular adverse events have been reported. Lowering the dose or administering the drug as a 5-minute infusion may increase safety.
Carbetocin, a synthetic oxytocin receptor agonist, has significantly longer half-life, and may reduce blood loss compared with oxytocin. The hemodynamic vasodilatory effects are comparable to oxytocin(1), but potential differences in adverse effects on myocardium are not well described yet.
Carbetocin has been in clinical use in EU since 2007, and the efficacy is documented in several RCTs. In the proposed study, carbetocin will be used within then conditions of the marketing authorization. Oxytocin is the first line treatment and prophylaxis in Norway and most countries in the world.
According to recently published guidelines from EU drug authorities (EMA), oxytocin should be given as a slow 5-minute infusion in order to avoid hypotension. This has so far not been implemented in Norway. The pre-clinical and clinical experience of the two drugs are summarized in the Summaries of Product Characteristics.

Pregnancy and delivery is a natural process, but for many women this period is stressful and not without risks of morbidity, and even mortality. Circulatory adverse events leading to death have been reported after intravenous injection of oxytocin(2). Some studies indicate that oxytocin may lead to dose dependant ischemic ECG changes(3, 4), prolongation of QT time and liberation of biomarkers of myocardial cell death(3).
Previously we have demonstrated comparable vasodilatory effects of oxytocin and carbetocin(1). There is no clinical study comparing the specific myocardial effects of oxytocin with carbetocin. It may have great impact on the choice of standard medication if the cardiotoxicity of carbetocin is lower compared with oxytocin. The study of potential cardiotoxicity has to be performed in healthy women. Knowing that millions of labouring women have had uneventful injections of oxytocin and carbetocin after delivery, there is probably no reason to fear long lasting negative effects of either drug. Improved knowledge about the effects of the two drugs on heart and circulation will aid treatment decisions especially for women with underlying heart disease or hypertensive complications of pregnancy, but even for healthy women undergoing caesarean delivery.

The aim of the pilot study is to compare 0h (before C-section), 4h, 10h and 24h plasma concentrations of troponin I (highly sensitive methods), troponin T, NT-proBNP, CK-MB and other relevant myocardial markers and ECG changes in elective healthy C-section patients randomized to oxytocin 2.5 U or carbetocin 100 µg, by 1-minute injection immediately after delivery.

Based on the results from the pilot trial, sample size calculation for the main trial (CMT2) will be performed to answer which of the drugs causes more release of high sensitive troponin I.

Some clinical studies indicate that administering carbetocin will influence pain perception. One clinical study comparing carbetocin and oxytocin for prevention of PPH after caesarean

delivery, reported significantly reduced pain intensity in patients receiving carbetocin(5). A secondary analysis of postoperative opioid consumption in another clinical trial comparing hemodynamic effects of oxytocin and carbetocin, found a tendency of lower consumption of opioids in the carbetocin group, but the differences were not statistically significant(6).
The CMT-pain trial, a substudy of the CMT trial, will be conducted to investigate group differences in reported pain intensity and opioid consumption. Information on the patients level of anxiety, depression and pain catastrophizing traits will be obtained prior to the operation. In addition, biobank material will be analysed for levels of inflammatory markers related to pain.

2.0 DATA SOURCE

2.1 Patients

We will conduct a double blinded randomized controlled trial where healthy women undergoing C-section will receive either oxytocin or carbetocin immediately after delivery of the baby. Ratio between the groups will be 1:1.

2.1.1 CMT pilot trial

Forty patients will be recruited from the general population of the birth clinics of Oslo University Hospital (OUH). Based on blinded analysis in this pilot trial, statistical power analysis and group size estimation will be performed to prepare for a larger confirmatory main trial (CMT2).

2.1.2 CMT2 trial

240 patients will be included into the CMT2 trial from the general population of the birth clinics of OUH and Akershus University Hospital (AHUS).

2.1.3 CMT pain trial

This trial will include 40 patients from the pilot trial and the first 40 patients from the CMT2-trial included at the birth clinic of OUH, Rikshospitalet.

2.2 Inclusion and exclusion criteria

Inclusion criteria are healthy pregnant women aged 18 to 50, singleton pregnancy at gestational age 36 weeks or more, who are able to read and understand Norwegian.
Patients with placenta pathology, bleeding disorders, organ failure, prolonged QT-time or other serious cardiac diseases, epilepsy or known intolerance to any of the two drugs will be excluded from entering the trial.

2.3 Follow-up and timing of measurements

Patients will be followed for a period of 48 hours after the administration of study drug.
In the pilot trial, blood samples will be drawn at 0h, before C-section (=baseline), and at 4h, 10h and 24h after delivery (=test drug administration). The myocardial biomarkers including high sensitive troponin I, troponin T, CK, CK-MB and NT-proBNP will be measured at all time points. If indicated by increase in some of the specific biomarkers, which will be analysed consecutively, an additional sample at 48h will be included.

During the C-section the patients will be attached to a Holter-monitor that will allow us to read ECG changes that are triggered by administration of test drug. The first ten minutes immediately following administration of study medicine will be evaluated for ST-segment changes, duration of ST-segment changes, prolonged QT-time and occurrence of arrhythmia. Data on ECG changes will be analysed only in the pilot trial.

In the CMT2 trial, blood samples of high sensitive troponin I and levels of sodium and hemoglobin will be measured at 0h and at an interval of 6-10h after study drug administration.

Data on uterine contraction, routine assessments of newborn status, side effects of test drug, consumption of analgesics and reported level of postoperative pain, nausea and tiredness will be obtained. Prior to the C-section patients will be asked to fill in standardized self-reporting forms designed to determine level of anxiety, depression and pain catastrophizing traits.

3.0 STUDY OBJECTIVES

3.1 Primary objectives

3.1.1 CMT pilot trial

To measure the difference between oxytocin and carbetocin in changes over time in Troponin I release from baseline to 24h after test drug administration, and ECG changes from baseline to 10 minutes after test drug administration.

3.1.2 CMT2 trial

To measure the difference between oxytocin and carbetocin in changes over time in Troponin I release from baseline to an interval of 6-10h after test drug administration.

3.1.3 CMT pain trial

To measure the difference between oxytocin and carbetocin in changes over time in opioid consumption and reported pain intensity from baseline to 48h after test drug administration.

3.2 Secondary objectives

Plasma levels of sodium, hemoglobin and myocardial biomarkers such as troponin T, CK, CK-MB and NT-proBNP will be analysed for group differences in changes over time.

A study biobank is established both for the CMT pilot trial and the CMT2 trial.

To measure the difference between oxytocin and carbetocin in: uterine tone, blood loss, perioperative side effects, postoperative pain and side effects, consumption of analgesics, ECG changes, and time consumption from time of delivery till end of surgery.

To describe the relationship between the preoperative reported level of anxiety, depression and pain catastrophizing trait and opioid consumption and pain intensity during the first 48 hours after caesarean delivery.

3.3 Explorative objectives

We expect further analysis to be performed on the data set that may generate separate analysis and publications.

3.4 Study design

The study is designed as a double-blinded randomized controlled trial including healthy singleton pregnant women undergoing Caesarean delivery. The participants will be randomized 1:1 to oxytocin 2.5 U or carbetocin 100µg, 1-minute injection immediately after delivery.

3.4.1 CMT pilot trial

40 patients will be included from the birth clinics of OUH.

3.4.2 CMT2 trial

240 patients will be included from the birth clinics of OUH and AHUS.

3.4.3 CMT pain trial

40 patients from the pilot trial and the first 40 patients from the CMT2 trial included at OUH, Rikshospitalet will be included in the trial.

4.0 HYPOTHESIS AND DECISION RULES

4.1 Primary endpoint and statistical hypotheses

The protocol is designed to investigate group changes over time in patients receiving carbetocin compared to oxytocin.

The primary null hypothesis states that there is no difference between the treatment groups. The alternative hypothesis states that the changes over time differ between the treatment groups.

4.1.1 CMT pilot trial

The primary endpoint of interest is the treatment difference in changes over time in high-sensitive troponin I levels, measured at baseline 4h, 10h, and 24h after drug administration.

4.1.2 CMT2 trial

The primary endpoint is the treatment difference in changes over time in high-sensitive troponin I levels, measured at baseline and at an interval of 6-10h after drug administration.

4.1.3 CMT pain trial

The primary endpoint is treatment difference in opioid consumption and reported pain intensity within the first 48h after test drug administration.

4.2 Statistical decision rule

The primary and all secondary outcomes will be analysed with two-sided tests and confidence intervals and a statistical significance level of 5%.

5.0 ANALYSIS SETS

5.1 Enrolled

The enrolled set will include healthy singleton pregnant women undergoing Caesarean delivery at the birth clinics at OUH or AHUS, who have provided informed consent and have been included into the study data base.

5.2 Full analysis set

The full analysis set will be defined as all enrolled patients randomly assigned to a treatment group having received the study drug.

The patients are included in the study at an interval of 1-14 days prior to the set date of the planned C-section. Some of the patients will go into active labor prior to the planned date, and some of the planned C-sections will be shifted to an inconvenient time point for study completion due to competing acute activity at the maternity ward. These patients will be included in the study, but will end their study participation prior to receiving the study drug. The same is true for patients requiring general anaesthesia due to inadequate effect of spinal anaesthesia.
A modified intention to treat analysis will be performed on all the patients included in the study having received the study drug.

5.3 Safety analysis set

The safety analysis set will be equal to the full analysis set.

5.4 Per protocol analysis set

The per protocol analysis set will include all randomised patients meeting the study eligibility criteria and with no major protocol deviations affecting the treatment efficacy.
Major protocol deviations include entering into active labor prior to set date of planned C-section, planned C-section shifted to an inconvenient time point for study completion due to competing acute activity at the maternity ward, and need for general anaesthesia due to inadequate effect of spinal anaesthesia.

5.5 Treatment misallocation

If patients were randomized but not treated, the patients will appear on the study flowchart as randomized but not treated. This is the extent of how much the patient will be reported.

5.6 Protocol deviation

The following sections describe any protocol deviations that relate to the statistical analyses and forms the requirements for exclusion from the PPS.

5.6.1 Deviations to inclusion and/or exclusion criteria

Any patient who enters the study when the inclusion or exclusion criteria would have prevented entry, will be considered to have had a protocol deviation.

5.6.2 Deviations assessed post-randomization

Any patient who withdraw their consent during the observation period of 48 hours following administration of study medicine.
Randomised patients that for any medical reason will be prevented from completing the study according to study protocol.

6.0 ASSESSMENT, DEFINITION AND DERIVED VARIABLES

6.1 Primary outcome: High sensitive troponin I

Level of troponin I is measured at baseline (before administration of test drug) and at fixed time points following administration of test drug, and is a continuous variable measured in ng/L.

6.1.1 CMT pilot trial

Level of troponin I is measured at baseline and at 4, 10, 24 and if necessary 48 hours after study drug administration.

6.1.2 CMT2 trial

Level of troponin I is measured at baseline and at an interval of 6-10 hours after study drug administration.

6.2 Secondary outcomes

6.2.1 Other myocardial biomarkers.

The following myocardial biomarkers will be analysed at the same time points in the CMT pilot trial.

- Troponin T, a continuous variable measured in ng/L. The lower detection level of troponin T is 5 ng/L.
- CK, a continuous variable measured in U/L.
- CK-MB, a continuous variable measured in µg/L. The lower detection level of CK-MB is 1 µg/L.
- NT-proBNP, a continuous variable measured in ng/L. The lower detection level of NT-proBNP is 50 ng/L.

All measurements of biomarkers below their detection limits will be randomly imputed from a uniform distribution with lower limit equal to 0 and upper limit equal to the detection limit.

6.2.2 Other blood analyses

The following analyses will be performed at the same time points as for analysis of troponin I, for the CMT pilot trial at 0, 4, 10 and 24 hours and for the CMT2 trial at 0 and 6-10 hours after study drug administration.

- Hemoglobin, a continuous variable measured in g/100ml.
- Sodium (Na), a continuous variable measured in mmol/L
- Biobank analyses, continuous variables measured in units according to the specific variable.

6.2.3 Uterine tone

Uterine tone will be evaluated by obstetrician in charge of the C-section at 2.5 and 5 minutes after test drug administration
A numeric rating scale ranging from 0-10 is used (0 = no effect, 7 = clinically satisfactory contraction, 10 = maximal uterus contraction). The variable will be treated as continuous in the statistical analyses.

In case of need for additional uterotonic agent(s) for adequate uterine tone, time to rescue medication will be reported as a continuous variable in minutes.

6.2.4 Blood loss

Blood loss will be estimated by the formula for calculated blood loss as published by Stafford, revised with weight in kg and height in cm(7).
A continuous variable measured in mL.

6.2.5 Perioperative side effects.

During the first 10 minutes after administration of test drug, the patient will be asked to report any side effects. Severity of side effects will be registered in time gaps as follows 0-2 min, 2-5 min and 5-10 min.
Severity of side effects is an ordered categorical variable:

- 0 = no side effects at the given point
- 1 = mild side effects
- 2 = moderate side effects
- 3 = severe side effects.

Treatment given to alleviate side effects (a binary variable) will be registered as

- 0 = no treatment administered
- 1 = treatment administered

6.2.6 Postoperative pain and side effects

Pain at rest, pain after coughing, nausea and tiredness will be registered at 4h, 10h, 24h and 48 h after administration of test drug in the CMT pilot trial..
A numeric rating scale ranging from 0-10 is used (0 = no discomfort, 10 = maximal discomfort imaginable). The variables will be treated as continuous in the statistical analyses.

6.2.7 Consumption of analgesics

Postoperative pain treatment protocol includes oral paracetamol 1 g and ibuprofen 400 mg 4 times daily and IV morphine administered by a patient controlled analgesia pump (PCA).
In the CMT pain trial, overall postoperative morphine consumption in mg will be measured, as well as morphine consumption in the time periods 0-4h, 4-10h, 10-24h and 24-48h after test drug administration.
A continuous variable measured in mg.

6.2.8 QOL forms detecting level of anxiety, depression and pain catastrophizing trait

Prior to the operation the patients will be asked to fill inn QOL forms detecting level of anxiety, depression and pain catastrophizing trait. Only in the CMT pain trial.

6.2.8.1 Modified three simple questions

A numeric rating scale ranging from 0-100 is used to rate anxiety, anticipated level of pain, need for analgesics and coping with motherhood (0 = not at all, 100 = to an extreme degree). The variables will be treated as continuous in the statistical analyses.

6.2.8.2 Pain Catastrophizing Scale (PCS)

PCS consists of 13 questions scored as follows.

- 0 = not at all
- 1 = to a slight degree
- 2 = to a moderate degree
- 3 = to a great degree
- 4 = all the time

The overall score is achieved by summarizing the scores of the 13 questions. Results from the PCS will range from 0-52. The variable will be treated as continuous in the statistical analyses.

A PCS score of ≥ 30 is considered to be associated with clinical relevance. Reported level of PCS ≥ 30 will be reported as a binary variable (PCS $< 30 = 0$, and PCS $\geq 30 = 1$).

6.2.8.3 Hopkins Symtom CheckList (HSCL-25)

HSCL-25 consists of 25 questions measuring level of anxiety and depression. Each question is scored as follows.

- 1 = Not at all
- 2 = A little bit
- 3 = Quite a bit
- 4 = Extremely

The value for HSCL-25 is obtained by calculating the mean score of the 25 questions. The variable will be reported as a continuous variable.

HSCL-25 of ≥ 1.75 is considered clinically relevant, and will be reported as a binary variable (HSCL-25 $< 1.75 = 0$, HSCL-25 $\geq 1.75 = 1$).

6.2.9 ECG changes

In the CMT pilot trial, the patients will be attached to a digital Holter monitor (Medilog AR4, Schiller) during the C-section to evaluate ECG changes during the first 10 minutes following administration of test drug.
The following parameters will be registered:

- Occurrence of ischemic episode (ST-segment depression of ≥ 0.1mV). Registered as a binary variable (no ischemic episode = 0, one/more ischemic episodes = 1)
- Duration of ischemic episode. Continuous variable measured in seconds.

- Degree of ST-segment depression from baseline. Continuous variable measured in mV.
- Beat to beat analysis of QT time corrected according to Framingham. Continuous variable measured in msec.
- Occurrence of arrhythmia. Registered as a binary variable (no episodes of arrhythmia = 0, one/more episodes of arrhythmia = 1)

6.2.8 Time consumption

Time consumption from time of delivery until end of surgery and from time of delivery to time of discharge form postoperative ward unit.
A continuous variable measured in minutes.

6.3 Summary of endpoints (TABLE)

OUTCOME	ENDPOINT	TYPE
Primary	Troponin I level	Continuous
Other myocardial markers	Troponin T level	Continuous
	CK level	Continuous
	CK-MB level	Continuous
	NT-proBNP level	Continuous
Other blood analyses	Hemoglobin level	Continuous
	Sodium level	Continuous
	Biobank analyses	Continuous
Uterine tone	Uterine tone	Continuous
	Time till rescue, min	Continuous
Blood loss	Calculated blood loss, ml	Continuous
Perioperative side effects	Severity of side effects	Ordered categorical
	Treatment of side effects	Binary
Postoperative pain and side eff.	Pain at rest	Continuous
	Pain after coughing	Continuous
	Nausea	Continuous
	Tiredness	Continuous
Consumption of analgetics	Morphine consumption, mg	Continuous
QOL forms	Modified three simple questions	Continuous
	PCS	Continuous
	PCS $\geq$ 30	Binary
	HSCL-25	Continuous
	HSCL-25 $\geq$ 1.75	Binary
ECG changes	Occurrence ischemic episode	Binary
	Duration ischemic episode, sec	Continuous
	ST-segment depression, mV	Continuous
	Prolonged QTc interval	Binary
	Beat to beat analyses QTc interval	Continuous
	Occurrence of arrhythmia	Binary
Time consumption	Time consumption, min	Continuous

7.0 STATISTICAL METHODOLOGY

7.1 Sample size determination

7.1.1 CMT pilot trial

The predefined main outcome variable in this double blinded randomized controlled study is group differences in changes over time in high sensitive troponin I levels. This is the first clinical study comparing these outcome measures and calculation of statistical power and group size estimations are not possible. After all data from 40 patients (1:1 group size) have been collected, a blinded analysis based on these study data will be performed by a medical statistician, who will get access to outcome measures and information about treatment allocation, but not the actual treatment. Unblinding will be performed when all analyses have been completed.

7.1.2 CMT2 trial

Based on preliminary results of the CMT pilot trial, the largest difference in plasma troponin I concentration was found at 10 hours, with a mean±standard deviation change from baseline of 0.41±0.79 ng/L in the carbetocin group versus a mean change of 1.78±4.48 in the oxytocin group. The sample size calculation was based on 80% power to detect a between-group difference in change from baseline to 10 hours of 1.37, to be analysed using a two-sample T-test with adjustments for unequal variances. With a significance level of 5%, we will need to include 178 patients (89 in each treatment group) in the CMT2 trial. To adjust for loss of information from missing values and patient drop outs, 240 women will be enrolled. The drop-out rate after enrolment is expected to be low as the duration of the study is short.

7.2 Randomization

After inclusion, patients will be randomized to one of two study arms. The randomization will be performed immediately before study start. The person responsible for preparing the study drug will be unblinded and not otherwise involved in patient treatment. Research personnel involved in patient treatment, data collection and analysis will not receive information about actual treatment allocation until all data has been collected and analyses have been completed. Randomization will be performed by a researcher not involved in the data collection. The randomization responsible will decide block size and if variable block size will be used.

7.3 Blinding

All study participants will be blinded to the treatment allocation with the exception of the person responsible for preparing the study drug and the person generating the randomization list. These persons will not be the same as the one responsible for analysis of the trial data. Blinding of study drug will be secured by using standard 5 ml syringes marked with date and randomization number according to study protocol.

7.4 Statistical methods

7.4.1 Primary and secondary analyses

The primary analysis will be a modified intention to treat analysis of the primary outcome (highly sensitive troponin I) on the full analysis set. We will initially perform a blinded analysis of the primary outcome.

Secondary analyses will be:

1. A per protocol analysis on the primary outcome (troponin I) on the per protocol analysis set
2. Modified intention to treat analyses of all secondary outcomes on the full analysis set
3. Sensitivity analyses to examine the impact of missing data (Section 7.4.5)

7.4.2 Repeated-measures continuous outcomes

The primary endpoint and all other continuous endpoints, including baseline and ≥1 follow-up measurements, will be analysed with linear regression models, with the follow-up measurement defined as the dependent variable and treatment group and baseline measurement defined as independent variables. Based on the fitted models, we will estimate treatment group differences in changes from baseline with 95% confidence intervals (CIs), together with a p-value for the null hypothesis of no treatment group difference. We expect at least some degree of skewness in the primary and some of the secondary endpoints, and maybe also in the residuals from the linear regression models. The amount of skewness will be assessed with histograms and descriptive statistics, such as mean, median, variance, and the skewness index. In cases where the distribution of the residuals deviates markedly from the normal distribution, or when the endpoints themselves are too skewed to use means as measures of central tendency, we will use median regression models instead of linear regression models, thus analysing between-group differences in median changes from baseline instead of mean changes from baseline. Standard errors and CIs in the median regression models will be obtained via bootstrapping with 100 replications.

7.4.3 Continuous outcomes measured at single time points

Continuous outcome variables measured at single time points will be analysed with two-sample t-tests (and 95% confidence intervals for the differences between means), with adjustment for unequal variances (the Welch U test). In situations where the distribution of the variable is difficult to assess or deemed to be highly skewed, median regression models will be used instead of t-tests to test and estimate differences in medians.

7.4.4 Categorical outcomes

Binary outcomes will be analysed with Fisher mid-P tests and Newcombe hybrid score confidence intervals for the difference between probabilities.

Ordered categorical outcomes will be analysed with score tests for effect in a proportional odds model (the Wilcoxon-Mann-Whitney test).

7.4.5 Handling of missing data

Due to a short interval of observation in the CMT trial, only 48 hours after test drug administration, we expect a low level of missing data in this trial.
For categorical outcomes and continuous outcomes measured at one or two timepoints, a complete case analysis will be the primary analysis. In addition, sensitivity analyses will be

performed for the primary outcome, where missing data will be imputed according to the following scenarios:

1. Best-case outcome in the oxytocin group and worst-case outcome in the carbetocin group.
2. Worst-case outcome in the oxytocin group and best-case outcome in the carbetocin group.

   Best case outcome = group mean + 2SD
   Worst case outcome = group mean - 2SD, levels below 0 are set to 0.

3. Group-specific mean values

Similar sensitivity analyses for missing data will be performed for other continuous and categorical secondary end points, if the proportion of missing outcome values is greater than 10%. Best and worst case for categorical variables will be the lowest or highest possible score according to each variable. For the binary variable occurrence of arrhythmia, for instance, best case score = 0 (no episodes of arrhythmia) and worst case score = 1 (one/more episodes of arrhythmia).

Continuous variables measured at more than two time points will be analysed with linear mixed models (Section 7.4.2), which automatically handle missing data under the missing at random assumption.

7.4.6 Statistical software

StataSE version 16 (StataCorp LLC, College Station, TX) will be used for all statistical analyses, except analyses of categorical outcomes, which will be done with MATLAB version R2019b (MathWorks, Inc.).

8.0 References

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