




## STUDY PROTOCOL

**REVISED** A study protocol for the cardiac effects of a single dose of either oxytocin 2.5 IU or carbetocin 100 µg after caesarean delivery: a prospective randomized controlled multi-centre trial in Norway [version 2; peer review: 2 approved]

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### Abstract

**Background:** Both oxytocin and carbetocin are used to prevent uterine atony and post-partum haemorrhage after caesarean delivery in many countries, including Norway. Oxytocin causes dose-dependent ST-depression, troponin release, prolongation of QT-time and arrhythmia, but little is known about myocardial effects of carbetocin. We have previously demonstrated comparable vasodilatory effects of oxytocin and carbetocin and are now undertaking a Phase 4 trial to investigate whether carbetocin causes similar changes to myocardial markers compared with oxytocin.

**Methods:** Our randomized controlled trial will be conducted at three obstetrics units at Oslo University Hospital and Akershus University Hospital, Norway. Planned enrolment will be of 240 healthy, singleton pregnant women aged 18 to 50 years undergoing planned caesarean delivery. Based on pilot study data, each participant will receive a one-minute intravenous injection of either oxytocin 2.5 IU or carbetocin 100 µg during caesarean delivery. The prespecified primary outcome is the change from baseline in high-sensitive troponin I plasma concentrations at 6–10 hours after study drug administration. Secondary outcomes include uterine tone grade at 2.5 and five minutes after study drug administration, adverse events for up to 48

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1

2

#### version 2

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[view](#)



[view](#)

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hours after study drug administration, estimated blood loss within eight hours of delivery, need for rescue treatment and direct/indirect costs. Enrolment and primary analysis are expected to be completed by the end of 2021.

**Discussion:** Women undergoing caesarean delivery should be assessed for cardiovascular risk particularly as women with an obstetric history of pregnancy induced hypertension, gestational diabetes mellitus, preterm birth, placental abruption, and stillbirth are at increased risk of future cardiovascular disease. Any additional ischaemic myocardial risk from uterotonic agents will need to be balanced with the benefit of reducing the risk of postpartum haemorrhage. Any potential cardiotoxicity difference between oxytocin and carbetocin will help inform treatment decisions for pregnant women.

**Registration:** Clinicaltrials.gov [NCT03899961](https://clinicaltrials.gov/ct2/show/study/NCT03899961) (02/04/2019).

### Keywords

Oxytocin, carbetocin, troponin I, anaesthesia, caesarean delivery, uterine atony

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**REVISED Amendments from Version 1**

Changes have been made in response to the peer-review comments, comprising clarification that our study follows a pilot study that explored the myocardial effects of oxytocin 2.5 IU and carbetocin 100 µg in 40 healthy women with singleton pregnancies who underwent a planned caesarean section; acknowledgement that little is known about the effects of carbetocin in myocardium animal models; echocardiogram was not performed as part of the screening process; clarification of the randomization process; clarification that study drug administration was in line with the current guidelines; adding a reference to support that the 11-point scale used to assess uterine tone has good interrater agreement; clarification that there is a planned sub-analysis for the primary endpoint for women who received the study drug and did not require rescue treatment for uterine atony; clarification that there is a planned sub-study to investigate any potential differences in postpartum pain experienced by women depending on whether they received oxytocin or carbetocin; explanation that although the study protocol was approved in 2019, the COVID-19 pandemic has slowed recruitment; and provided additional details of what is known about the effects of oxytocin on myocardium.

**Any further responses from the reviewers can be found at the end of the article**

**Abbreviations**

AE: adverse event  
 AHUS: Akershus University Hospital  
 CI: confidence interval  
 CTCAE: Common Terminology Criteria for Adverse Events  
 IU: international unit  
 IV: intravenous  
 mmHg: millimetre of mercury  
 OUH: Oslo University Hospital  
 PMI: perioperative myocardial injury  
 SAP: statistical analysis plan

**Introduction**

Oxytocin receptor agonists, including oxytocin and carbetocin, are recommended for prevention and treatment of postpartum haemorrhage. Women who undergo caesarean delivery are at risk of excessive postpartum bleeding caused by uterine atony. Prophylactic administration of intravenous (IV) oxytocin to prevent uterine atony is standard first-line practice after caesarean delivery in many countries, including Norway.<sup>1,2</sup> Nevertheless, serious cardiovascular adverse events, including ST segment depression, hypotension and tachycardia have been reported after IV oxytocin.<sup>2</sup> Women with long QT syndrome type 2 have a particularly high postpartum risk of lethal arrhythmias.<sup>3</sup> Oxytocin dose reduction and/or increased infusion duration may reduce risk of some cardiac-related adverse effects and increase patient safety.<sup>2</sup>

Carbetocin, a synthetic oxytocin receptor agonist with a significantly longer half-life than oxytocin, reduces postpartum blood loss by stimulating uterus contraction.<sup>4-6</sup> Carbetocin has been in clinical use for the prevention of postpartum haemorrhage in Europe since 1999, and a room-temperature stable formulation has been available since 2015.<sup>7</sup> The efficacy is documented in several randomized controlled trials and meta-analyses.<sup>5,8-10</sup> Although both oxytocin and carbetocin have similar haemodynamic effects,<sup>11-13</sup> there is insufficient evidence of their comparable effects on the myocardium. Cardiac troponin I is a protein that is released by myocardial myocytes when starved of oxygen and can be used as an indirect measure of ischaemic heart damage. Perioperative myocardial injury can be defined as elevated or increased cardiac troponin I plasma concentration, with or without additional ischaemic signs or symptoms.<sup>14</sup> High-sensitivity detection assays can be used to monitor normal ranges of plasma troponin I concentrations.<sup>15</sup>

To our knowledge little data have been published on the effect of carbetocin on myocardium in animal models. As both oxytocin and carbetocin are used daily in obstetric units all over the world, we find it compelling to investigate whether the myocardial effects of oxytocin and carbetocin are comparable in healthy women undergoing caesarean delivery.

**Aims and objectives**

Following a pilot study that enrolled 40 women (NCT02528136), the aim of this follow-on Phase 4 trial is to determine any potential differences between oxytocin 2.5 IU and carbetocin 100 µg in their myocardial effects by measuring plasma troponin I using a high-sensitivity assay in a larger sample of healthy women with a singleton pregnancy undergoing a planned caesarean delivery. Plasma concentrations will be collected before caesarean delivery and 6–10 hours after study drug administration. Other endpoints relating to uterus tone, blood loss, blood pressure, heart rate, post-operative pain and side effects will also be assessed.

## Protocol

The study is a parallel group, randomized, patient- and investigator-blinded Phase 4 study. Enrolment of participants started in April 2019 and completed in February 2022. The protocol has been approved by the Regional Committee for Medical Research Ethics and the Norwegian Medicines Agency, and is being conducted according to the Good Clinical Practice principles that have their origins in the Declaration of Helsinki. The trial was registered at [Clinicaltrials.gov](https://clinicaltrials.gov) (NCT03899961) in April 2019.

## Ethics approval and consent to participate

The project has approval from the Regional Committee for Medical and Health Research Ethics (REC 2014/1210), The Norwegian Medicines Agency and the Institutional Data Protection officer at Oslo University Hospital. Signed informed consent form and expected cooperation of the participants for treatment and follow-up will be obtained and documented according to the International Council of Harmonisation-Good Clinical Practice (ICH GCP), and national/local regulations.

## Study setting

Women will be recruited from the general population at the three birth clinics at Oslo University Hospital (two clinics) and Akershus University Hospital in Norway.

## Eligibility criteria

All participants will have a normal singleton pregnancy at gestational age of 36 weeks or more, and will be able to read and understand Norwegian. Women with common comorbid diagnoses (diabetes, hypothyreosis, hypertension, etc) and pregnancy after *in vitro* fertilization will also be eligible for enrolment. Women will be excluded from enrolment if they have any of the following: placenta praevia or invasive placenta; pre-eclampsia; a bleeding disorder, such as von Willebrand disease type I; current treatment with low-molecular-weight heparin or other anticoagulation medication (not including aspirin); any known intolerance to either of the study drugs; prolonged QT-time or other serious cardiac disease; liver or kidney failure; epilepsy; or any medical reason why, in the opinion of the investigator, the patient should not participate. ECG was not part of the screening criteria.

## Recruitment

A total of 240 healthy pregnant women aged between 18 and 50 years will be included in our trial. Signed informed consent form and expected cooperation of the participants for treatment and follow-up will be obtained and documented according to the International Council of Harmonisation-Good Clinical Practice (ICH GCP), and national/local regulations. All data pertaining each enrolled participant will be entered into the electronic clinical report file (eCRF; Viedoc<sup>®</sup>, Uppsala, Sweden).

## Screening

Potentially eligible participants will be screened for inclusion after their last consultation before their scheduled delivery by the principal investigator from each study site. Oral and written information about the trial will be provided to each woman at least 24 hours before delivery and written informed consent obtained before randomization. Consent, participation and redraw of consent will be documented in electronic patient record. All screened women, including those who do not give consent to participate in the study, will be registered by number. Screened women who are not enrolled due to exclusion criteria or non-fulfilment of inclusion criteria will be registered by number and the reason for not participating in the study will be recorded.

## Randomization and blinding

Participants will be randomized 1:1 to receive either oxytocin 2.5 IU or carbetocin 100 µg after caesarean delivery. The patients will be randomized according to a computer-generated list of random numbers, with permuted blocks of different sizes unknown to the researchers. Each eligible woman who has given consent to participate in the study will be assigned a randomization number in consecutive order. The randomization number is linked to the randomization list as an integral part of Viedoc – the eCRF solution. Test assessing the blinding for each responsible investigator will be performed.

Although the standard procedure according to its label is to administer 1 mL of carbetocin (100 µg/mL),<sup>7</sup> to maintain treatment masking, both study drugs will be diluted to 5 mL using normal saline by a trained member of staff otherwise uninvolved with the trial, and labelled with the trial identification and randomization number according with ICH GCP and local regulations.

## Study drug dosage and administration

A single dose of either oxytocin 2.5 IU (Syntocinon<sup>®</sup>, Swedish Orphan Biovitrum, Stockholm, Sweden) or carbetocin 100 µg (Pabal<sup>®</sup>, Ferring Pharmaceuticals, St-Prex, Switzerland) will be administered by the investigator (a trained anaesthetist) as a one-minute IV injection immediately after delivery of the baby's head and shoulders. IV oxytocin 2.5 IU is standard dose used prophylactically at our institutions. Both oxytocin and carbetocin are used prophylactically after delivery to prevent uterine atony and excessive blood loss. The dosing of the study drugs is in line with the recommended dosing regimens which stipulate oxytocin up to 3 IU and carbetocin up to 100 µg should be administered over a time period of more than 30 seconds.<sup>2</sup>

## Prespecified analyses

### *Primary endpoint*

The primary endpoint is the difference between the oxytocin 2.5 IU and carbetocin 100 µg treatment groups in change from baseline in high-sensitive troponin I plasma concentrations 6–10 hours after study drug administration. Details of laboratory testing are provided below.

### *Secondary outcomes*

Uterine tone will be assessed at 2.5 minutes and five minutes after study drug administration, using a numerical rating scale 0–10, where 0 = no tonus and 10 = maximum tonus, and 7 = clinically satisfactory tonus, and  $\leq 6$  correlates well with the need for rescue treatment.<sup>13</sup> The obstetricians performing the caesarean delivery will be presented with the scale prior to starting the procedure. The scale has good interrater agreement.<sup>16</sup> Blood loss will be estimated by volume during the surgical procedure as well as calculating estimated blood loss based on haematocrit percentage within 24 hours after delivery, height and weight prior to caesarean delivery.<sup>17</sup>

Postoperative pain during the first 48 hours after delivery will be assessed in a sub-study of 80 women at one centre to further investigate any differences in postpartum/post-operation pain for the two study drugs. For these women, pain intensity (numerical rating scale 0–10) and opioid consumption (time and dose) will be recorded. In addition to the standard pain-relief treatment, these patients will have a patient-controlled intravenous morphine pump.

Direct and indirect healthcare costs will be assessed. Direct costs will include administered study drugs and any rescue treatment of uterine atony required, as well as costs to treat blood loss, and side effects of the therapeutic interventions. Indirect costs include the number of hours staff spend with patients in theatre and in post-anaesthesia care unit.

### *Vital signs monitoring*

Vital signs and baseline blood tests (haemoglobin and sodium concentrations) of participating women will be recorded prior to administration of anaesthesia. Throughout each caesarean delivery, there will be continuous monitoring of vital signs, including echocardiogram, blood pressure and heart rate.

Routine assessments of neonatal status will be recorded (Apgar 1 and 5 minutes, umbilical vein and artery acid-base status).

## Safety assessments

The participants will be informed about the expected adverse events (AEs) prior to study enrolment and instructed to score grade of AEs at 0–2, >2–5 and >5–10 minutes after the start of study drug administration, when the majority of AEs are expected to occur. Each participant will be instructed to inform the investigator immediately if they manifest any signs or symptoms they perceive as AEs the following 48 hours (duration of the trial). Unexpected serious adverse events will be reported, also after this period, until discharge from the hospital. All AEs will be recorded according to the Common Terminology Criteria for Adverse Events version 4.0 (CTCAE).

Suspected unexpected serious adverse reactions that result in death, are immediately life-threatening, require hospitalisation, result in persistent or significant disability or incapacity, will be reported immediately to the health authorities. Other suspected serious unexpected adverse reactions will be reported in an unblinded manner to the health authorities as soon as possible but within a maximum of 15 days of first knowledge by the Sponsor (Oslo University Hospital). In order to keep the Investigator and other persons generating data to the study blinded to treatment group, the unblinding and the reporting will be performed by the clinical trial unit at Oslo University Hospital, who is also responsible for monitoring the trial and randomization.

### *Expected adverse events*

Expected AEs are feeling of warmth, chest pain, shortness of breath, palpitations, flushing, headache, nasal congestion, xerostomia, and metallic taste. Both drugs in the study will lead to vasodilatation with a decrease in blood pressure and an increase in heart rate. The causal relationship of each AE to the study medication will be assessed by the investigators as either unrelated, unlikely to be related, possibly or probably related or definitely related.

### Concomitant medication

#### *Rescue medication*

In case of uterus atony, patients will be treated with rescue oxytocin 1 IU every 2 minutes up to maximum 5 IU in addition to the administration of the study drug (oxytocin 2.5 IU or carbetocin 100 µg). If there is still need for additional uterotonic treatment, this will be provided according to departmental procedures, and may include administration of prolonged oxytocin infusion, methylergometrine, prostinphenem, misoprostol or surgical or mechanical intervention as required. Time of rescue medication administration and dose will be recorded. Any additional treatment required, whether medical or surgical, will be decided by the attending obstetrician and anaesthesiologist according to local guidelines.

#### *Anaesthesia and pain medication*

Spinal anaesthesia will be given according to study procedure (2 mL bupivacaine [5 mg/mL] + 0.4 mL fentanyl [50 µg/mL]), hypotension prophylaxis (0.5 µg/kg IV phenylephrine [0.1 mg/mL] followed by infusion rate 0.25 µg/kg/min) and IV volume (isotonic saline) 10 mL/kg starting concomitantly with spinal anaesthesia. Spinal induced hypotension (systolic arterial pressure <90 mmHg) will be treated with an extra IV bolus of phenylephrine if the heart rate is above 60 beats/min or with IV ephedrine 5–10 mg if 60 beats/min or below. Analgesic medication will be administered as required by the participants and will include oral paracetamol 1 g and oral ibuprofen 400–600 mg four times per day. Patients may be given one IV bolus ketorolac trometamol 30 mg and IV bolus or oral oxycodon administered according to local guidelines and as required by the participants.

All medication interventions, including drug dose and time of administration will be recorded.

### Criteria for patient discontinuation

Patients may be discontinued from study treatment and assessments at any time. Specific reasons for discontinuing a patient for this study are as follows: (1) Voluntary discontinuation by the patient who is at any time free to discontinue her participation in the study, without prejudice to further treatment; (2) Severe non-compliance to protocol as judged by the principal investigator; (3) Incorrect enrolment i.e., the patient does not meet the required inclusion/exclusion criteria for the study. Patients who withdraw or are withdrawn from the study, will stop further treatment. Reasons for discontinuation will be documented.

### Laboratory tests

Blood samples from participating women will be collected at baseline (prior to caesarean delivery) and between six and 10 hours after study drug administration. Haemoglobin and sodium concentrations will be assessed using the point-of-care blood gas analyser(s) (ABL 800 Analyzer<sup>®</sup>, Radiometer, Copenhagen, Denmark). Blood plasma samples, stored in a certified research biobank freezer (–70 °C), will be analysed centrally for troponin I concentration as one batch at the Vestre Viken Trust, Drammen Hospital, Norway, once the last participant has completed the study. Plasma Troponin I concentrations for each participant will be measured using high-sensitive detection with a chemiluminiscent microparticle immunoassay (Alinity i<sup>®</sup>, Abbott, Illinois, U.S.A.). Normal values of troponin I in a female population (age 18 to 50 years) should be <15 ng/L, with the cut-off corresponding to the 99 percentile of a healthy reference population.<sup>18–20</sup> Recently, high-sensitivity circulating Troponin T <14 ng/L was deemed sufficient for ruling out myocardial ischaemia among 196 pregnant women and after delivery, and that elevated levels mandated further attention on cardiac symptoms.<sup>21</sup>

### Data collection and monitoring

Every investigator responsible for entering data into the eCRF will be provided with a unique identity and password, thereby creating an electronic signature of the investigator attesting the accuracy of the data on each eCRF. If any assessments are omitted, the reason for such omissions will be noted on the eCRFs. Corrections, with the reason for the corrections if applicable, will be dated and signed by the investigator in the eCRF. Electronic files, including the data from CRF entered into an electronic database software will be stored at the research server at Oslo University Hospital. This

data storage is administered by the Data Inspectorate's local representative. The patient identification and the code list will be kept by the principal investigator in a locked office, ensuring confidentiality. Investigators involved with data analysis will have access to the study data base. Patient files will be kept for the maximum period of time permitted by each hospital.

The Clinical Study Monitor, independent from the investigators, will visit each investigator regularly to will check and collect completed CRFs, discuss the progress of the study and monitor drug usage according to ICH GCP guidelines. The monitoring will also include source data verification (data audit). A data monitoring committee will not be used as the data collection is expected to be straightforward. Authorized representatives of a regulatory authority and Ethics Committee may visit the centre to perform inspections, including source data verification.

### Power and sample size considerations

The sample size required for our current study was calculated using data from a pilot study of 40 patients, in which the largest difference in plasma troponin I concentration was found at 10 hours, with a mean  $\pm$  standard deviation change from baseline of  $0.41 \pm 0.79$  ng/L in the carbetocin group versus  $1.78 \pm 4.48$  in the oxytocin group. The sample size calculation was thus 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%, our study will need to include 178 patients (89 in each treatment group) in this confirmatory trial. To adjust for loss of information from missing values and patient dropouts, 240 women will be enrolled. The drop-out rate after enrolment is expected to be low as the duration of the study is short.

### Analysis plan

The primary endpoint and all other continuous endpoints that include baseline and  $\geq 1$  follow-up measurement(s) 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 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.

Continuous endpoints measured at a single time point will be analysed with two-sample T tests and 95% CIs for the difference between means based on the t distribution, with adjustment for unequal variances. Median regression will be used for variables with highly skewed distributions.

Binary outcomes will be analysed with Fisher mid-P tests and Newcombe hybrid score confidence intervals for the difference between probabilities.<sup>22</sup> Ordered categorical outcomes will be analysed with score tests for effect in a proportional odds model (the Wilcoxon-Mann-Whitney test).<sup>22</sup>

All analyses will be performed on the modified intention-to-treat population, comprising all patients included in the trial who received the study drug. AEs and vital signs will be presented with descriptive statistics. In addition, the primary endpoint will also be analysed in a sub-population that will comprise all participants who receive their allocated study drug and who do not require rescue treatment for uterine atony. Further details of the statistical methods, including definitions of the intention-to-treat and per protocol populations, how to handle missing data, and sensitivity and exploratory analyses are available in the Statistical Analysis Plan (SAP) available on the trial registration page.

### Data dissemination plan

The results of the study will be published in an open-access peer-reviewed journal and deposited at the [trial registration page](#). Requests for data sharing/case pooling may be directed to the project Principal Investigator: Professor Rosseland on email: [rossela@ous-hf.no](mailto:rossela@ous-hf.no).

### Study status

The trial is actively recruiting at all sites.

## Discussion

Both oxytocin and carbetocin are used routinely after caesarean delivery to prevent uterine atony and excessive blood loss.<sup>5,8</sup> We know that oxytocin causes dose-dependent ST-depression, troponin release, prolongation of QT-time and arrhythmia, but little is known about myocardial effects of carbetocin.<sup>23</sup> Our ongoing study has been designed to assess high-sensitivity troponin I plasma concentrations after the prophylactic administration of either oxytocin or carbetocin to determine whether there are any differences in their myocardial effects. The protocol of this parallel, randomized, blinded phase 4 study has been approved by the Regional Committee for Medical Research Ethics and the Norwegian Medicines Agency, and follows the principles for Good Clinical Trial practice. In addition, the biobank has been approved by the Regional Committee for Medical Research Ethics for storage of blood plasma from the participating women. Although patients started being enrolled in 2019 when the study started, recruitment has been hindered by the COVID-19 pandemic. All enrolled women will have the same techniques performed for their caesarean delivery, comprising a Pfannenstiel skin incision. Once the baby and placenta have been delivered, exteriorization of the uterus will be performed according to local guidelines. This will limit confounding variables of different surgical techniques interference with assessment of uterine tone. The primary endpoint of change in troponin I (high-sensitive detection method) will be analysed after the final participant has completed the trial as one batch, therefore the results will not influence any participant's treatment, including rescue treatment with oxytocin, or follow-up.

Although the use of oxytocin has reduced the risk of postpartum haemorrhage, its haemodynamic effects may cause ECG changes relating to myocardial ischaemia at doses of 10 IU compared with methlergometrine 0.2 mg.<sup>24</sup> The same study included a control group of 10 non-pregnant patients who received oxytocin 10 IU who developed similar ECG changes, showing that the myocardial effects are related to oxytocin administration and not to pregnancy, surgical procedure, delivery, or sympathetic block from spinal anaesthesia.<sup>24</sup> Carbetocin, a synthetic derivate of oxytocin but with a longer half-life (median terminal elimination half-life is 33 minutes after intravenous administration and 55 minutes after intramuscular administration<sup>7</sup>) shows similar haemodynamic effects to oxytocin.<sup>11-13</sup> Like oxytocin, carbetocin binds to the oxytocin receptor therefore affects the same tissues.<sup>7</sup> Oxytocin has been shown to increase cardiac output by decreasing vascular tone in small and peripheral arteries, resulting in a lower blood pressure and a compensatory increase in heart rate, implying increased myocardial oxygen demand.<sup>25</sup> Carbetocin also increases cardiac output.<sup>13</sup> Minor differences have been detected in the recovery times for heart rate and blood pressure changes, with heart rate elevations lasting slightly longer with carbetocin, possibly related to the longer half-life of carbetocin compared with oxytocin.<sup>11,13</sup>

There is some uncertainty about the clinical implications of transient troponin release. Transient high sensitive troponins I and T can be measured after physical activity, such as endurance activities such as marathons, or even after short bursts of strenuous physical activity.<sup>26</sup> There is some concern that exercise-induced increases in troponin may not be a benign physiological response to exercise, but an early marker of future mortality and cardiovascular events.<sup>27</sup> Moreover, perioperative myocardial injury (PMI) is an important but often undetected complication on noncardiac surgery as it rarely is accompanied by typical symptoms of myocardial ischaemia, such as chest pain, or dyspnea.<sup>14</sup> Although PMI is common after noncardiac surgery (approximately 16% of patients with a median age of 74 years),<sup>14</sup> little is known about the risk of PMI in women undergoing caesarean delivery. One small study of 26 women showed troponin I plasma concentrations suggestive of myocardial ischaemia 12-hours post caesarean delivery.<sup>28</sup> All 26 women had received postpartum intravenous oxytocin (10 IU, over 30 seconds),<sup>28</sup> which is a much higher dose than our current study, in which women will be randomized to receive a one-minute intravenous infusion of either oxytocin 2.5 IU or carbetocin 100 µg. Nevertheless, the clinical relevance is that PMI appears to increase post-operative mortality risk. In a prospective cohort study of nearly 22,000 people undergoing in-patient noncardiac surgery, a peak postoperative high sensitivity troponin T increase of at least 5 ng/L during the first three days after surgery was significantly associated with 30-day mortality even if there were no ischaemic signs or symptoms (adjusted hazard ratio, 4.69; 95% CI, 3.52–6.25).<sup>29</sup> A smaller study of 2018 patients undergoing nearly 3000 surgical procedures also showed that a preoperative to postoperative increase of  $\geq 14$  ng/L of high-sensitivity troponin T (detected in 285 patients) was associated with increased mortality at 30-days (9.8% of patients with PMI versus 1.6% without PMI) and at one-year (22.5% of patients with PMI versus 9.3% without PMI).<sup>14</sup> Our study will assess high-sensitivity troponin I levels as we expect very small levels of troponin release in response to either oxytocin or carbetocin. Currently, the Abbott troponin I immunoassay has a lower limit of detection of 0.1 ng/L whereas the Roche troponin T immunoassay has a higher lower limit of detection of 5.0 ng/L.<sup>30</sup> Our baseline assessments will help provide a reference range of troponin I for pregnant women at term. All troponin I measurements below 0.1 ng/L will be designated as 0 ng/L.

## Strengths and limitations

The study design is robust, the sample size based on *a priori* power calculations with parameters estimated from recent, relevant pilot data, and the trial will be conducted in a representative sample of pregnant women at three Norwegian birth clinics. Our study is enrolling women from general obstetric practice, including those with comorbidities such as



gestational diabetes and hypertension. There is no upper limit for body mass index for participating women, and with an upper age limit of 50 years, nearly all women with singleton pregnancies at the three clinics will be eligible for inclusion. Women aged between 18 and 50 years make up approximately 25% of the Norwegian population.<sup>31</sup> Although this is not an international study, many other countries in Europe have similar obstetric practices.

In 2019, a core outcomes set was published for prevention of post-partum haemorrhage to aid better comparison of clinical trials ensuring a minimum of outcomes to be reported.<sup>32</sup> Our protocol was approved prior to its publication. Nevertheless, our study will assess seven out of nine of the core outcomes (blood loss, shock, transfer to higher level of care, use of additional haemostatic interventions and adverse events). We will not assess breastfeeding or patient satisfaction with treatment, but will report pain and pain relief medication.

All caesarean deliveries will be performed with standardized anaesthesia and surgery, including the meticulous blood pressure control to reduce cardiac troponin I due to spinal anaesthesia-induced hypotension and/or tachycardia. Both intraoperative tachycardia and hypotension are associated with myocardial injury after noncardiac surgery,<sup>33</sup> thereby, we are limiting an important confounding factor that may complicate the interpretation of our results.

As all participating women have to be able to read and understand Norwegian in order to provide informed consent, this may limit generalizability to diverse ethnic background to some extent. We will provide detailed demographic and baseline characteristics of all participating women.

In the analyses of direct and indirect costs, any potential drug specific long-term cardiac adverse events rate will not be included. We expect differences in health care costs between oxytocin and carbetocin cost to be minor.

### Interpretation

Women with an obstetric history of pregnancy induced hypertension, gestational diabetes mellitus, preterm birth, placental abruption, and stillbirth are at increased risk of future cardiovascular disease.<sup>34,35</sup> Women undergoing caesarean delivery should be assessed for cardiovascular risk. Any additional ischaemic myocardial risk from uterotonic agents administered postpartum need to be balanced with the benefit of reducing the risk of postpartum haemorrhage. We anticipate that data from our study will help future clinical management decisions around planning delivery in pregnant women, including those with heart disease. As far as we can tell, no other study has compared the myocardial effects of oxytocin and carbetocin when used as postpartum uterotonic agents after caesarean delivery. We currently know little about troponin release after vaginal delivery and the role of uterotonics on troponin release in this population, which would require further investigation.

### Conclusion

The results of our trial will help inform treatment decisions around preventing uterine atony in women undergoing caesarean delivery.

### Data availability

#### Extended data

Zenodo: Supporting material for article 'A study protocol for the cardiac effects of a single dose of either oxytocin 2.5 IU or carbetocin 100 µg after caesarean delivery: a prospective randomized controlled multi-centre trial in Norway', <https://doi.org/10.5281/zenodo.5217789>.<sup>36</sup>

This project contains the following extended data:

- Ethics approval CMT2014 REC English translation.pdf
- Norwegian Medicines Agency approval SLV-godkjenning CMT-studien English included.pdf
- Pasientinformasjon - v3.pdf
- Protocol v8 signed.pdf

## Reporting guidelines

Zenodo: SPIRIT and TIDieR checklists for 'A study protocol for the cardiac effects of a single dose of either oxytocin 2.5 IU or carbetocin 100 µg after caesarean delivery: a prospective randomized controlled multi-centre trial in Norway', <https://doi.org/10.5281/zenodo.5519494>.<sup>36</sup>

Data are available under the terms of the [Creative Commons Attribution 4.0 International license](https://creativecommons.org/licenses/by/4.0/) (CC-BY 4.0).

## Acknowledgements

The authors wish to thank the members of the study group at Akershus University Hospital (AHUS) and Oslo University Hospital (OUH) for their excellent support which enables data collection and completion of this study; Hanne Helene Johnsen, Hanne Wickstrøm, Thomas Günther, Ellen Støvland Fjuk and Else-Marie Ringvold at AHUS, Eldrid Langesæter, Anders Krogh, Anders Aasheim and Ida Kristin Larsson Gerø at OUS-Rikshospitalet and Charlotte Loennechen, Thomas Heyerdahl, Bjarne Røed, Tomas Drægni and Camilla Smith at OUH-Ullevål. The persons acknowledged have given their permission hereto.

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# Open Peer Review

Current Peer Review Status:  

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Version 1

Reviewer Report 01 November 2021

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**Kim Ekelund** 

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## Review #2

Thank you for the opportunity to review this manuscript.

The main objective of this study was to compare the cardiac effect, measured as the increased level of Troponin I, after intravenous administration of Oxytocin 2.5IU or Carbetocin 100µg during cesarean section (CS) in healthy, singleton pregnant women aged 18 to 50 years undergoing planned caesarean. The prespecified primary outcome was change from baseline in high-sensitive troponin I plasma concentrations at 6–10 hours after study drug administration. Secondary outcomes include uterine tone grade at 2.5 and five minutes after study drug administration, adverse events for up to 48 hours after study drug administration, estimated blood loss within eight hours of delivery, need for rescue treatment, and direct/indirect costs.

**Overall**, the manuscript is well written, easy to read, and thoroughly describes a protocol for a Norwegian potentially clinically relevant RCT.

I have a few general comments. The protocol is registered on Clinicaltrials.gov as NCT03899961 and is referred to as Carbetocin Myocardium Trial 2014 Part 2 (CMT2014/2). The authors have also registered The Clinical Carbetocin Myocardium Trial (CMT) as NCT02528136.

This study is in the manuscript described as a pilot study including 40 patients. Moreover, the study is funded by the manufacturer of Carbetocin: Ferring Pharmaceuticals, including funding of medical writing support for this manuscript. Although it is stated "The funders had no role in study design, data collection, and analysis, decision to publish, or preparation of the manuscript", I will as a reader be more skeptical compared to a non-funded protocol. However, the protocol describes this openly and no conflicts of interest can be identified.

Finally, I understand the study already are up and running. ("Study status: The trial is actively recruiting at all sites.", and on Clinicaltrials.gov: September 30, 2021, is registered as Final data collection date for primary outcome measure). This makes me wonder, why I am asked to review a

protocol now, and not in 2019 before recruitment began?

Just more wondering: Has the cardiac effect of Oxytocin / Carbetocin been studied in an animal model? Has it been studied in non-pregnant adults? Can Troponin I be measured after physical activity (walking staircases, jogging, or similar)?

I have more **additional specific comments and questions:**

**“Protocol.** The study is a parallel-group, randomized, patient- and investigator-blinded Phase 4 study. Enrolment of participants started in April 2019 and is anticipated to be completed by the end of 2021...”

- Does this mean, that we are reviewing a protocol already in action?

**“Eligibility criteria.** All participants... (but not) prolonged QT-time or other serious cardiac diseases.

- Do you do a pre-CS echocardiography before inclusion? Or just during CS?

**“Randomization and blinding.** Participants will be randomized 1:1... to a computer-generated list of random numbers, with block sizes unknown”...

- Can you provide us with a more detailed description of the randomization? It sounds like a Viedoc@ is a black box? No description can be found regarding the “integral part of Viedoc – the eCRF solution”.

**“Study drug dosage and administration** A single dose of either Oxytocin 2.5 IU (Syntocinon®, Swedish Orphan Biovitrum, Stockholm, Sweden) or Carbetocin 100 µg ... will be administered by the investigator (a trained anesthetist) as a one-minute IV injection.

- Administering 2.5 IU of Oxytocin as a one-minute injection seems to be fast, and faster than the recommendations. We recommend an injection of 1IE/minute, or slower.
- Administering 100mikrog carbetocin diluted to 5ml as a one-minute iv injection also seems too fast. Should be administered slower than 1 minute.
- If the approximate ED95 for Oxytocin for elective CS is 0.35 IU and 15 µg for Carbetocin, shouldn't we test these dosages?
- In Ref 4 (Widmer *et al.*)<sup>1</sup> Oxytocin 10IU with Carbetocin 100µg is compared, They find 0.04 vs 0.09% that complains of chest pain, respectively, i.e., after a smaller dose of Carbetocin compared to what is used in this study. Have the authors considered reducing the Carbetocin dose?

**“Prespecified analyses.** *Secondary outcomes* Uterine tone will be assessed at 2.5 minutes and five minutes after study drug administration, using a numerical rating scale 0–10, where 0 = no tonus and 10 = maximum tonus, and 7 = clinically satisfactory tonus.”

- Do the obstetricians get any training in using this scale? Do they have a Gold Standard to compare with?

“Postoperative pain during the first 48 hours after delivery will be assessed in a subgroup of

women at one centre.”

- Why is this relevant? And if relevant, why is this only done in one centre?

“Direct and indirect healthcare costs will be assessed”.

- Will the costs of 10 IU Oxytocin (approx. 2 €) and 100 µg Carbetocin (approx. 40€) be included in the assessment?

**“Concomitant medication Rescue medication** In case of uterus atony, patients will be treated with rescue oxytocin 1 IU every 2 minutes up to maximum 5 IU.”

- Is it max 5 IU in total (ie 2.5 + 1 + 1 + 0.5 ??) or is it in addition to the 2.5?
- What happens after the maximum 5 IU is administered and there still is some atony?
- Will the additional Oxytocin not disturb the picture when comparing to Carbetocin – are these women excluded from getting Troponin I measured after 10 hours?

**“Laboratory tests....**Normal values of troponin I in a female population (age 18 to 50 years) should be <15 ng/L, with the cut-off corresponding to the 99 percentile of a healthy reference population. 17”

- In ref. 17 (Bahadur *et al*)<sup>2</sup>, the Pakistan population had a median age of the included female on 56 years old with the oldest being 86 and youngest being 21 years old. Most of the people 246 (82.3%) were above 40 years old. This means that they were older than the Norwegian CS population, and Troponin I increase with age, according to ref. 15, Venge *et al* .<sup>3</sup> Do the authors have any comments on this?
- Do we know if the Pakistan women have a similar Troponin level as Norwegian?
- What was the baseline level in the pilot study?
- Is Troponin I the best measurement for myocardial injury?
- What about proBNP?
- If all the levels are < the 99<sup>th</sup> percentile i.e. normal, can we then state that Carbetocin and Oxytocin are safe (regarding cardiac side-effects)?
- If there are minor differences but still within normal ranges, then this might not be clinically relevant? Like studies showing significant difference in blood loss on i.e., 178mL between treatment A and B... Significant - yes. Relevant - no! Any comments?

**“Power and sample size considerations.** The sample size required for our current study was calculated using data from a pilot study of 40 patients, in which 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 1.78 +/- 4.48 in the Oxytocin group”.

- I admit I am not used to doing statistical analysis, but does this mean that the change from the baseline can be 0.4ng/L – 0.8ng/L = -0.4ng/L? Because then Carbetocin improves the cardiac effect, reducing the Troponin I level? And similar for Oxytocin?
- Or does this mean that the data is skewed? And is “Median” not preferred instead of

“Mean”?

- What is the baseline for Oxytocin and Carbetocin, respectively?
- Is this because the authors suspect the results to be clinically not relevant, although detecting significant differences?
- And is this because Ferring is funding the project? (As I mentioned in the beginning, the reader should be more suspicious).

#### **Analysis plan**

- I believe I do not have enough knowledge to comment relevantly on the analysis plan.

**Strength and Limitations.** In 2019, a core outcome set was published for the prevention of postpartum hemorrhage to aid better comparison of clinical trials ensuring a minimum of outcomes to be reported...We will not assess breastfeeding or patient satisfaction with treatment, but will report pain and pain relief medication.”

- Why is this relevant to the study?
- Is the dose of Oxytocin 2.5IU used elsewhere?
- The cardiovascular events that are described after oxytocin iv dose (ST-changes, hypotension, tachycardia), have they been found after 2.5 IU?
- Will data be released at the person level (for i.e. reviewer) in case of potential cardiac damage, and high Troponin I level during the CS?

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**Is the rationale for, and objectives of, the study clearly described?**

Partly

**Is the study design appropriate for the research question?**

Yes

**Are sufficient details of the methods provided to allow replication by others?**

Partly

**Are the datasets clearly presented in a useable and accessible format?**

Not applicable

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Obstetric anesthesiology

**We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.**

Author Response 31 Mar 2022

**Leiv Arne Rosseland**, Oslo University Hospital, Oslo, Norway

01 Nov 2021 | for Version 1

**Kim Ekelund**, Department of Obstetrics, Juliane Marie Centre, Rigshospitalet, Copenhagen, Denmark

**Kim Lindelof**, Department of Anesthesiology, Juliane Marie Centre, Rigshospitalet, Copenhagen, Denmark

Reviewer comments are in *italicized* text. Author responses are in **bold** text.

**Comment**

*Thank you for the opportunity to review this manuscript.*

*The main objective of this study was to compare the cardiac effect, measured as the increased level of Troponin I, after intravenous administration of Oxytocin 2.5IU or Carbetocin 100µg during cesarean section (CS) in healthy, singleton pregnant women aged 18 to 50 years undergoing planned caesarean. The prespecified primary outcome was change from baseline in high-sensitive troponin I plasma concentrations at 6–10 hours after study drug administration. Secondary outcomes include uterine tone grade at 2.5 and five minutes after study drug administration, adverse events for up to 48 hours after study drug administration, estimated blood loss within eight hours of delivery, need for rescue treatment, and direct/indirect costs.*

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*This study is in the manuscript described as a pilot study including 40 patients. Moreover, the study is funded by the manufacturer of Carbetocin: Ferring Pharmaceuticals, including funding of medical writing support for this manuscript. Although it is stated "The funders had no role in study design, data collection, and analysis, decision to publish, or preparation of the manuscript", I will as a reader be more skeptical compared to a non-funded protocol. However, the protocol describes this openly and no conflicts of interest can be identified.*

**Author response**

**Studies require funding and we have been transparent about where our funding has**



come from. We are ensuring that the safety profiles in relation to the release of cardiac markers of two commonly used drugs are characterized fully so that clinicians will be able to make informed treatment decisions. We will report the results of this trial so that clinicians will be able to use our findings in order to improve standard of care for all women requiring prophylaxis treatment to prevent post-partum haemorrhage.

Our pilot study manuscript is currently undergoing peer-review at another journal.

#### **Comment**

*Finally, I understand the study already are up and running. ("Study status: The trial is actively recruiting at all sites."; and on Clinicaltrials.gov: September 30, 2021, is registered as Final data collection date for primary outcome measure). This makes me wonder, why I am asked to review a protocol now, and not in 2019 before recruitment began?*

#### **Author response**

We decided to write a protocol manuscript describing the Carbetocin Myocardium Trial 2014 part 2 (CMT 2) in January 2021 when we started writing our manuscript for the Pilot study. Our rationale for publishing the protocol is to increase awareness that oxytocin and carbetocin may have slightly different effects on the myocardium. At the point we decided to publish the protocol in more detail we had already started enrollment. The enrollment progress has been delayed due to the COVID-19 pandemic. Ideally this protocol article would be published prior to recruiting patient. We hope that readers will find the protocol and intention of our clinical trial valuable when making assessments of which uterotonic agent to use.

#### **Comment**

*Just more wondering: Has the cardiac effect of Oxytocin / Carbetocin been studied in an animal model? Has it been studied in non-pregnant adults? Can Troponin I be measured after physical activity (walking staircases, jogging, or similar)?*

#### **Author response**

The potentially harmful effects of oxytocin on heart tissue and circulation have been known for decades. The risk of such effect can to some extent be reduced by lowering the dose and increasing duration of IV injection. Notwithstanding, oxytocin receptor agonists are the recommended drug of choice for prevention and treatment of PPH. Indeed, PPH remains the leading cause of maternal death. Carbetocin has gained popularity during the recent years due to the prolonged duration of action. To our knowledge, little data exist on the effect of carbetocin on the myocardium in animal models. As both oxytocin and carbetocin are used daily at the described doses in obstetric units all over the world, we find it compelling to investigate whether the myocardial effects of oxytocin and carbetocin are comparable in healthy women undergoing caesarean delivery of their baby, even if the myocardial effects of carbetocin are not well described in animal models. We have amended the last paragraph of the Introduction to state more clearly that although there are no animal models, the myocardial effects of oxytocin and carbetocin warrant further

investigation.

Although animal models are lacking, there are studies that assessed the effects of oxytocin on heart tissue in pregnant women. The effect of oxytocin was studied in a clinical trial conducted by Svanström et al., including women undergoing cesarean delivery, investigating differences in the effect of oxytocin 10 IU and methylergometrine 0.2 mg on ECG changes related to myocardial ischemia. Clinically relevant occurrence of ECG changes were found in the oxytocin group, but not in the methylergometrine group. A control group of 10 non-pregnant patients receiving 10U of oxytocin also developed similar ECG changes. The authors conclude that the effects are related to oxytocin administration and not to pregnancy, surgical procedure, delivery, or sympathetic block from spinal anaesthesia (Svanström et al. 2008).

The clinical relevance of transient troponin release is still unknown. High-sensitive troponins, both troponin I and troponin T, can be measured after physical activity like prolonged endurance activities as marathon but also after short-term and intermittent exercise like 30min of running and basketball (Gresslien and Agewall 2016). There is some uncertainty on the clinical implication of these transient troponin release. However, there is increasing concern that exercise-induced increases in troponin may not be a benign physiological response to exercise, but an early marker of future mortality and cardiovascular events (Aengevaeren et al. 2019).

We have amended the manuscript (second paragraph of the 'Discussion') to include the above information.

#### **Comment**

*I have more additional specific comments and questions:*

*"Protocol. The study is a parallel-group, randomized, patient- and investigator-blinded Phase 4 study. Enrolment of participants started in April 2019 and is anticipated to be completed by the end of 2021..."*

- *Does this mean, that we are reviewing a protocol already in action?*

#### **Author response**

**Yes, we have started enrollment of the study. Please see the response to a similar comment above.**

#### **Comment**

*"Eligibility criteria. All participants... (but not) prolonged QT-time or other serious cardiac diseases.*

- *Do you do a pre-CS echocardiography before inclusion? Or just during CS?*

#### **Author response**

**In our clinic screening the patients with electrocardiogram is not a routine part of the**

preparation of patients for caesarean delivery. Patients with known cardiac disease or prolonged QT-time will be considered non-eligible for study participation. Thus, the participants are not screened with a pre-CS echocardiography to be included in the study. We have added that ECG was not part of the screening process to the section 'Eligibility criteria'.

**Comment**

*"Randomization and blinding. Participants will be randomized 1:1... to a computer-generated list of random numbers, with block sizes unknown"...*

- *Can you provide us with a more detailed description of the randomization? It sounds like a Viedoc@ is a black box? No description can be found regarding the "integral part of Viedoc – the eCRF solution".*

**Author response**

**We have amended the article to include a better description of the randomization process.**

**Comment**

*"Study drug dosage and administration A single dose of either Oxytocin 2.5 IU (Syntocinon®, Swedish Orphan Biovitrum, Stockholm, Sweden) or Carbetocin 100 µg ... will be administered by the investigator (a trained anesthetist) as a one-minute IV injection.*

- *Administering 2.5 IU of Oxytocin as a one-minute injection seems to be fast, and faster than the recommendations. We recommend an injection of 1IE/minute, or slower.*
- *Administering 100mikrog carbetocin diluted to 5ml as a one-minute iv injection also seems too fast. Should be administered slower than 1 minute.*

**Author response**

**Administration of oxytocin analogues is performed with great variety both nationally and internationally. There has been a shift from bolus dosing toward short infusion in case of IV administration. Thomas et al. showed that 5U oxytocin as a rapid bolus (approximately 1 second) induce more powerful hemodynamic effects compared to 5U administered as a 5-minute infusion (Thomas et al. 2007). However, little data exist comparing a 1-minute injection with a 5-minute infusion.**

**In our clinic the current practice is to administer either oxytocin 2.5 IU or carbetocin 100 µg as a 1-minute IV infusion. This is well within the recommended dosage regimen suggested in the guidelines published by Heesen et al in Anaesthesia in 2019, recommending that doses of oxytocin up to 3 IU or carbetocin up to 100 mg should be administered over a time period of more than 30 seconds (Heesen et al. 2019). Moreover, Dell-Kuster et al proved no advantage on haemodynamic stability of administering 100mg Carbetocin IV as a 5-minute infusion compared to a 1-minute injection (Dell-Kuster et al. 2017).**

**We have amended the article to include a statement that the duration of the injection of the study drugs was in line with current guidelines.**

**Comment**

- *If the approximate ED95 for Oxytocin for elective CS is 0.35 IU and 15 µg for Carbetocin,*

*shouldn't we test these dosages?*

#### **Author response**

It is well known that ED95 (the dose required to achieve the desired effect in 95% of the population) for oxytocin analogues are well below doses used in clinical practice for prevention of PPH in elective caesarean delivery. We still think it is important to investigate the difference in haemodynamic and myocardial effects of oxytocin and carbetocin at doses used in current clinical practice. Comparing myocardial effects of 0.35 IU of oxytocin and 15 mg of carbetocin will be an interesting topic for further studies. We have not made any amendments with regard to this comment.

#### **Comment**

- *In Ref 4 (Widmer et al.) Oxytocin 10 IU with Carbetocin 100 µg is compared. They find 0.04 vs 0.09% that complains of chest pain, respectively, i.e., after a smaller dose of Carbetocin compared to what is used in this study. Have the authors considered reducing the Carbetocin dose?*

#### **Author response**

To our knowledge, Widmer et al. are comparing the effect of oxytocin 10 IU administered intramuscularly (IM) with carbetocin 100 mg IM for the prevention of PPH after vaginal delivery. The dose of 100 mg of carbetocin is identical to the dose used in our study, the only difference is the route of administration, IV instead of IM. Widmer et al. found that 0.04% of patients in the oxytocin group complained of chest pain compared to 0.09% in the carbetocin group, however the group differences were not significant. We have not made any amendments with regard to this comment.

#### **Comment**

*"Prespecified analyses. Secondary outcomes Uterine tone will be assessed at 2.5 minutes and five minutes after study drug administration, using a numerical rating scale 0-10, where 0 = no tonus and 10 = maximum tonus, and 7 = clinically satisfactory tonus."*

- *Do the obstetricians get any training in using this scale? Do they have a Gold Standard to compare with?*

#### **Author response**

The obstetricians are presented with the 11-point numerical rating scale of uterine tone prior to the operation. A similar scale has been used in several clinical studies to determine level of uterine tone numerically (Sarna et al. 1997, Rosseland et al. 2013, Tabl et al. 2019). In our experience a uterine tone of 6 or less correlate well with the need for rescue uterotonic. Recently Cole et al. published an article concluding that the 0 to 10 numerical rating scale for uterine tone may be a reliable, standardized tool for research in reporting degree of uterotonic contraction during cesarean delivery (Cole et al. 2021). We have added a statement to the article to include the Cole et al 2021 citation in the section 'Secondary outcomes'

#### **Comment**

*"Postoperative pain during the first 48 hours after delivery will be assessed in a subgroup of women at one centre."*

- *Why is this relevant? And if relevant, why is this only done in one centre?*

#### **Author response**

Group differences in reported pain and opioid consumption will be further investigated in a sub-study including 80 patients. We have amended the manuscript to make it clearer that there is a pain sub-study. 80 patients were deemed sufficient to see if there is a difference in post-operative pain experienced by participating women. Pain experienced by people is very subjective, and many factors affect the levels of pain a person may experience. We decided to conduct the pain sub-study just in one centre to remove as many confounding variables as possible. If the 80 women in the sub-study were distributed across the three centres, we would not be sure whether there were other external factors at play, not just the study drugs.

#### **Comment**

*"Direct and indirect healthcare costs will be assessed".*

- *Will the costs of 10 IU Oxytocin (approx. 2 €) and 100 µg Carbetocin (approx. 40€) be included in the assessment?*

#### **Author response**

For estimation of direct and indirect healthcare costs, the costs of oxytocin and carbetocin will be included in the assessment along with the costs of rescue uterotonics, need for transfusions and duration of patient occupation of the operating room and the post-anaesthesia care unit after administration of study drug. We have made some minor edits to the article to clarify the direct and indirect healthcare costs.

#### **Comment**

**"Concomitant medication** *Rescue medication In case of uterus atony, patients will be treated with rescue oxytocin 1 IU every 2 minutes up to maximum 5 IU."*

- *Is it max 5 IU in total (ie 2.5 + 1 + 1 + 0.5 ??) or is it in addition to the 2.5?*
- *What happens after the maximum 5 IU is administered and there still is some atony?*
- *Will the additional Oxytocin not disturb the picture when comparing to Carbetocin – are these women excluded from getting Troponin I measured after 10 hours?*

#### **Author response**

Rescue medication with 1 IU of oxytocin for treating uterine atony will be administered every 2 minutes up to a maximum of 5 IU, in addition to either study drug (2.5 IU oxytocin or 100 mg carbetocin). In case there is still a need for additional uterotonic treatment, this will be provided according to departmental procedures, including administration of prolonged oxytocin infusion, methylergometrine, prostinphenem, misoprostol or surgical or mechanical intervention as required. We have amended the article under the section 'Rescue medication' to clarify this point.

The analysis of group differences in troponin I release will be performed in the

modified intention-to-treat population, comprising all participants receiving allocated test drug. In addition, we will conduct a pre-planned sub-analysis including all participants receiving allocated test drug but not requiring rescue drugs. We have added the sub-analysis to the fourth paragraph of the 'Analysis plan' as this was previously omitted by mistake.

#### **Comment**

**"Laboratory tests....**Normal values of troponin I in a female population (age 18 to 50 years) should be <15 ng/L, with the cut-off corresponding to the 99 percentile of a healthy reference population. 17"

- In ref. 17 (Bahadur et al)<sup>2</sup>, the Pakistan population had a median age of the included female on 56 years old with the oldest being 86 and youngest being 21 years old. Most of the people 246 (82.3%) were above 40 years old. This means that they were older than the Norwegian CS population, and Troponin I increase with age, according to ref. 15, Venge et al. <sup>3</sup> Do the authors have any comments on this?
- Do we know if the Pakistan women have a similar Troponin level as Norwegian?
- What was the baseline level in the pilot study?
- Is Troponin I the best measurement for myocardial injury?

#### **Author response**

It is well known that level of high-sensitive troponins in healthy patients vary with age and sex. During recent years, the 99<sup>th</sup> percentile cut-off for normal circulating concentration of high-sensitive troponin I (cTnI) has been lowered to <15 ng/L. This corresponds well to the findings of Kimenai et al. investigating 1540 individuals in a healthy European reference population (age 57±8 years, 52.4% women). Overall 99<sup>th</sup> percentile upper reference limits of cTnT and cTnI were 15 and 13 ng/L, respectively (Kimenai et al. 2016). Bossard et al published 99<sup>th</sup> percentile cut off for normal high-sensitive troponin I in a young healthy European population of 2077 adults from the general population aged 25–41 years without cardiovascular disease. The 99<sup>th</sup> percentile of cTnI was 15.79 ng/L in men and 5.11 ng/L in women (Bossard et al. 2017). Kimenai et al. also found that cardiac troponin concentrations differ in women and men and are stronger predictors of cardiovascular events in women (Kimenai et al. 2021).

The baseline level of cTnI in the pilot study was detected within the normal limits in all but one patient.

Recently Furenäs et al. published a study investigating dynamics of NTproBNP and cTnT in 196 healthy pregnant women. They found that existing cut-off values for ruling out heart failure (NTproBNP <300 ng/L) and myocardial ischaemia (hs-cTnT <14 ng/L) are applicable during pregnancy and after delivery, and that elevated levels mandate further attention on cardiac symptoms and renal function (Furenäs et al. 2020). We have amended the text in section 'Laboratory tests' to explain these points and added additional supporting references.

High-sensitive troponin is the preferred tool for detecting myocardial stress and injury. In our clinic the lower detection limit of cTnT is 5 ng/L whereas levels of cTnI down to 0.1 ng/L were detected in our material. By choosing cTnI we are able to describe even small changes in high-sensitive troponin more accurately in a healthy population of young women.

**Comment**

- *What about proBNP?*

**Author response**

Dynamics of NTproBNP was investigated in the pilot trial. We found no group differences in the development of NTproBNP and for this reason we decided not to proceed with measurements of NTproBNP in the CMT2 trial.

**Comment**

- *If all the levels are < the 99<sup>th</sup> percentile i.e. normal, can we then state that Carbetocin and Oxytocin are safe (regarding cardiac side-effects)?*
- *If there are minor differences but still within normal ranges, then this might not be clinically relevant? Like studies showing significant difference in blood loss on i.e., 178mL between treatment A and B... Significant - yes. Relevant - no! Any comments?*

**Author response**

We have reason to believe that even small elevations of high-sensitive troponins in relation to non-cardiac surgery are of clinical interest. Devereaux et al. investigated 21,842 adult patients undergoing non-cardiac surgery, mean age 63.1±10.7 years and 49.1% were female. They found that an absolute hsTnT change of 5 ng/L or higher was associated with an increased risk of 30-day mortality (Devereaux et al. 2017). Although in this study participants were much older than in our study, we believe that transient elevations may indicate subclinical myocardial injury that may result in a higher risk of future cardiovascular event that may be treatable or preventable. We have not made any specific amendments to this comment, but refer to our earlier response that transient elevations in troponins after physical activity may be an early marker for cardiovascular events.

**Comment**

***“Power and sample size considerations.*** *The sample size required for our current study was calculated using data from a pilot study of 40 patients, in which 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 1.78+/-4.48 in the Oxytocin group”.*

- *I admit I am not used to doing statistical analysis, but does this mean that the change from the baseline can be 0.4 ng/L – 0.8ng/L = -0.4 ng/L? Because then Carbetocin improves the cardiac effect, reducing the Troponin I level? And similar for Oxytocin?*
- *Or does this mean that the data is skewed? And is “Median” not preferred instead of*

"Mean"?

**Author response**

The measurements of cTnI in our pilot study were skewed, and therefore best described by median and range, however for sample size calculations mean values and standard deviations are used.

**Comment**

- *What is the baseline for Oxytocin and Carbetocin, respectively?*

**Author response**

The baseline cTnI values for both the oxytocin and carbetocin groups in the Pilot study were similar.

**Comment**

- *Is this because the authors suspect the results to be clinically not relevant, although detecting significant differences?*

**Author response**

We started the pilot study not knowing whether there would be any difference between oxytocin and carbetocin in their cardiac effects but as oxytocin is known to affect the myocardium, we thought it was worth investigating given that carbetocin has a longer duration of action than oxytocin. As both oxytocin and carbetocin are used for PPH prophylaxis treatment, if it turns out that one has a less pronounced effect on the myocardium, this will help make clinical decisions for pregnant women with heart disease.

**Comment**

- *And is this because Ferring is funding the project? (As I mentioned in the beginning, the reader should be more suspicious).*

**Author response**

We have been transparent in the study's funding and Ferring's role in the study.

**Comment**

**Analysis plan**

- *I believe I do not have enough knowledge to comment relevantly on the analysis plan.*

***Strength and Limitations.*** *In 2019, a core outcome set was published for the prevention of postpartum hemorrhage to aid better comparison of clinical trials ensuring a minimum of outcomes to be reported...We will not assess breastfeeding or patient satisfaction with treatment, but will report pain and pain relief medication."*

- *Why is this relevant to the study?*



**Author response**

The core outcome set for the prevention of PPH has been established to allow easier comparison of clinical trials studying prevention of PPH. The core outcome set was published after our protocol was approved. The relevance to our study is that we are assessing seven out of nine recommended core outcomes, except for breastfeeding and patient satisfaction. The core outcome set includes intention and maintenance of breastfeeding as important patient-centred outcome as PPH may trigger a series of events that prevent or reduce a mother's ability to fully breastfeed, particularly if the mother and baby are separated. It is also worth noting that breastfeeding releases oxytocin and therefore affects uterus tone but there is insufficient evidence for whether breastfeeding reduces PPH risk.

**Comment**

- *Is the dose of Oxytocin 2.5 IU used elsewhere?*
- *The cardiovascular events that are described after oxytocin iv dose (ST-changes, hypotension, tachycardia), have they been found after 2.5 IU?*

**Author response**

No one has yet published the cardiovascular effects of oxytocin 2.5 IU IV. We have investigated this dose in our pilot study and will add the citation once it has been published.

**Comment**

- *Will data be released at the person level (for i.e. reviewer) in case of potential cardiac damage, and high Troponin I level during the CS?*

**Author response**

We are batch assessing high-sensitivity troponin I levels after the last patient has completed the trial, which means that all patients will received standard of care. Follow-up is for 48 hours after their caesarean delivery. We will not know whether individual patients have high Troponin I levels during their hospital stay. Further studies will be required to determine risk of cardiovascular events due to PPH prophylaxis treatment, if there is indeed any future risk.

**Comment**

- *Is the rationale for, and objectives of, the study clearly described?*

Partly

- *Is the study design appropriate for the research question?*

Yes

- *Are sufficient details of the methods provided to allow replication by others?*

Partly

- *Are the datasets clearly presented in a useable and accessible format?*

Not applicable

**Author response**

**No response necessary.**

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**Competing Interests:** No competing interests were disclosed.

Reviewer Report 26 October 2021

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**Pamela J. Angle**

Sunnybrook Research Institute, Toronto, Canada

The protocol describes a parallel, blinded, two-arm randomized controlled safety trial which aims to examine the myocardial effects of intravenous carbetocin (100mcg ) versus oxytocin (2.5units), given over 1 minute immediately after elective cesarean delivery. Rescue therapy will include the use of oxytocin as necessary in both groups (up to 5 units). The study will recruit 240 women, with single gestation pregnancies greater than 36 weeks, and without medical comorbidities (e.g. hypertension, diabetes), from three university-affiliated clinics in Norway. Women will receive standardized management of spinal anesthesia, the fluid co-load, and vasopressors. The primary endpoint will be changes in high sensitivity Troponin I levels, measured at baseline preoperatively and 6-10 hours after drug administration between groups as well as other important secondary outcomes, including severe adverse events, measured up to 48 hours after delivery. Differences in pain between groups will be assessed at one study site. Women will receive multimodal analgesia and intravenous patient-controlled opioid analgesia. Given that oxytocin is a first line drug for the prevention of uterine atony and postpartum hemorrhage, the variability with which it is currently dosed, and the rising age and co-morbidities found in childbearing women in developed countries, study findings may have important implications for the management of patients at higher cardiac risk during cesarean section.

The Spirit checklist was previously (2018) completed by the authors during protocol development but some elements of the trial design and conduct remain unclear. Protocols available on other trial registry websites provide much of the additional information required. The study is funded, in

part, by an unrestricted grant from the makers of Carbetocin. The authors note that funders had no role in study design, data collection, and analysis, decision to publish, or preparation of the manuscript.

It should be made clear early in the protocol that the current safety Trial builds on the authors' previous pilot work (randomized controlled trial, n=40) to provide the reader with more context. The pilot study demonstrated a reduction in changes in high sensitivity Troponin I levels from baseline with Carbetocin( 0.41+/-0.79ng/L ) compared with oxytocin (1.78 +/-4.48 ng/L) after elective cesarean delivery. It also showed that changes in high sensitivity Troponin I peaked 10 hours after drug administration when the primary outcome of the current trial is to be measured. [Protocol Synopsis, The Clinical Carbetocin Myocardium Trial- Part II<sup>1</sup>]. Information provided in the sample size estimation section suggests that the study is powered as a superiority trial aimed at confirming findings of the previous pilot work.

Additional details and clarification related to trial organization and how the trial is run from day to day at the three sites are required. The role of the clinical trials unit mentioned seems to be limited to the generation of the randomization schedule and oversight/monitoring of the trial itself.

Please provide additional information related to randomization (e.g. were random permuted blocks of different sizes used? As reported, the person making up study drugs was the only person who knew treatment assignments. As reported, the PI screened potential candidates across all three sites for eligibility. Who consented patients? How exactly were patients allocated to treatment arms? Was this internet-based using Viedoc also? Were baseline Troponin I levels available for any of the patients prior to treatment allocation or were these also batched with the 6-10 hour samples for testing? Is there any plan to assess the blinding of the anesthetist involved in patient care during the c-section?

The primary analysis will be by modified intention to treat. The primary outcome will be assessed using an independent student t-test followed by regression modeling. It appears the authors assume that randomization will balance any known confounders (e.g. women with hypertension, diabetes) between treatment arms. It will be important to assess whether any significant difference found in the primary outcome holds up after adjusting for imbalances.

## References

1. Leiv Arne Rosseland: The Clinical Carbetocin Myocardium Trial – Part II. [Reference Source](#)

### **Is the rationale for, and objectives of, the study clearly described?**

Partly

### **Is the study design appropriate for the research question?**

Yes

### **Are sufficient details of the methods provided to allow replication by others?**

Yes

### **Are the datasets clearly presented in a useable and accessible format?**

Not applicable

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Anesthesiology, Health Research Methodology, Obstetrical anesthesia

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.**

Author Response 31 Mar 2022

**Leiv Arne Rosseland**, Oslo University Hospital, Oslo, Norway

PROTOCOL MANUSCRIPT - Review

26 Oct 2021 | for Version 1

**Pamela J. Angle**, Sunnybrook Research Institute, Toronto, Canada

Reviewer comments are in *italicized* text. Author responses are in **bold** text.

#### **Comment 1**

*The protocol describes a parallel, blinded, two-arm randomized controlled safety trial which aims to examine the myocardial effects of intravenous carbetocin (100mcg ) versus oxytocin (2.5units), given over 1 minute immediately after elective cesarean delivery. Rescue therapy will include the use of oxytocin as necessary in both groups (up to 5 units). The study will recruit 240 women, with single gestation pregnancies greater than 36 weeks, and without medical comorbidities (e.g. hypertension, diabetes), from three university-affiliated clinics in Norway. Women will receive standardized management of spinal anesthesia, the fluid co-load, and vasopressors. The primary endpoint will be changes in high sensitivity Troponin I levels, measured at baseline preoperatively and 6-10 hours after drug administration between groups as well as other important secondary outcomes, including severe adverse events, measured up to 48 hours after delivery. Differences in pain between groups will be assessed at one study site. Women will receive multimodal analgesia and intravenous patient-controlled opioid analgesia. Given that oxytocin is a first line drug for the prevention of uterine atony and postpartum hemorrhage, the variability with which it is currently dosed, and the rising age and co-morbidities found in childbearing women in developed countries, study findings may have important implications for the management of patients at higher cardiac risk during cesarean section.*

*The Spirit checklist was previously (2018) completed by the authors during protocol development, but some elements of the trial design and conduct remain unclear. Protocols available on other trial registry websites provide much of the additional information required. The study is funded, in part, by an unrestricted grant from the makers of Carbetocin. The authors note that funders had no role in study design, data collection, and analysis, decision to publish, or preparation of the manuscript.*

*It should be made clear early in the protocol that the current safety Trial builds on the authors' previous pilot work (randomized controlled trial, n=40) to provide the reader with more context. The pilot study demonstrated a reduction in changes in high sensitivity Troponin I levels from*

baseline with Carbetocin( 0.41+/-0.79ng/L ) compared with oxytocin (1.78 +/-4.48 ng/L) after elective cesarean delivery. It also showed that changes in high sensitivity Troponin I peaked 10 hours after drug administration when the primary outcome of the current trial is to be measured. [Protocol Synopsis, The Clinical Carbetocin Myocardium Trial- Part II<sup>1</sup>]. Information provided in the sample size estimation section suggests that the study is powered as a superiority trial aimed at confirming findings of the previous pilot work.

#### **Author response**

**We have added text to the 'Aims and objectives' to state that the protocol of this current study has followed a pilot study. The pilot study is not currently published as it is undergoing journal review.**

#### **Comment**

*Additional details and clarification related to trial organization and how the trial is run from day to day at the three sites are required. The role of the clinical trials unit mentioned seems to be limited to the generation of the randomization schedule and oversight/monitoring of the trial itself.*

#### **Author response**

**We have amended the text to state that the principal investigator from each study site screened women for inclusion in the study.**

#### **Comment**

*Please provide additional information related to randomization (e.g. were random permuted blocks of different sizes used? As reported, the person making up study drugs was the only person who knew treatment assignments. As reported, the PI screened potential candidates across all three sites for eligibility. Who consented patients? How exactly were patients allocated to treatment arms? Was this internet-based using Viedoc also? Were baseline Troponin I levels available for any of the patients prior to treatment allocation or were these also batched with the 6-10 hour samples for testing? Is there any plan to assess the blinding of the anesthetist involved in patient care during the c-section?*

#### **Author response**

**We have amended the article to better describe the organization of randomization in Viedoc and assessment of blinding and allocation of patients. We have clarified that test assessing each responsible investigator will be performed in the 'Randomization and blinding' subsection.**

**Baseline troponin I levels were not assessed prior to randomization. All troponin I levels were batch assessed and none of the investigators will have access to these results until after the last patient has completed the study. No changes have been made with regard to assessment of troponin I levels as these are explained in the subsection 'Laboratory tests'**

#### **Comment**

*The primary analysis will be by modified intention to treat. The primary outcome will be assessed*

using an independent student *t*-test followed by regression modeling. It appears the authors assume that randomization will balance any known confounders (e.g. women with hypertension, diabetes) between treatment arms. It will be important to assess whether any significant difference found in the primary outcome holds up after adjusting for imbalances.

- **Is the rationale for, and objectives of, the study clearly described?**

Partly

- **Is the study design appropriate for the research question?**

Yes

- **Are sufficient details of the methods provided to allow replication by others?**

Yes

- **Are the datasets clearly presented in a useable and accessible format?**

Not applicable

#### **Author response**

**We have added a few sentences at the end of the 'Introduction' to provide more clearly the rationale for conducting the study. In addition, we have provided more information about the statistical analysis as we will conduct additional prospective sub-analysis of patients who did not receive rescue treatment in cases of uterine atony as this may change the results.**

**Competing Interests:** No competing interests were disclosed.

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