Nordic randomized trial on laparoscopic versus vaginal cerclage

Acronym: NORACT

TRIAL PROTOCOL

Version 13.0
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ClinicalTrials.gov number: not yet available

Trial sponsor:
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Contents

1. Title

Nordic randomized trial on laparoscopic versus vaginal cerclage (NORACT)

2. Trial approvals & registration

The trial will be registered at clinicaltrials.gov using the administrative authorities of Aarhus University (UAarhus).
The study will be subjected to approval by The Central Denmark Region Committees on Health Research Ethics.

3. Protocol version 13

4. Funding

The trial is investigator-initiated. The Novo Nordic Foundation has funded the trial with approx. 10 million DKK. The funding is administered at the Department of Gynecology & Obstetrics, Aarhus University Hospital, Denmark and can be used for salary for named collaborators, data handling, and additional operational expenses according to the funding terms. Private and public funds will be sought for additional costs if necessary. The funding agencies will have no role in any aspects of conducting and reporting of the trial.

5. Roles and responsibilities

Primary investigator

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The NORACT board

Julie Glavind (DK)
Kirsten Hald (NO)
Lea Kirstine Hansen (DK)
Hulda Hjartardóttir (ISL)
Oskari Heikinheimo (FI)
Bo Jacobsson (SE)
Pernille Tine Jensen (DK)
Lise Qvirin Krogh (DK)
Helena Karypidis (SE)
Andrew Shennan (UK)
Niels Uldbjerg (DK) Chair
The NORACT board is decisive but respects that Niels Uldbjerg is the trial sponsor and responsible for the reporting to the NOVO Nordic foundation.

National coordinating investigators

Each participating country has one (or two) national coordinating investigator to fulfill specified national responsibilities in the country they represent and to act on its behalf as primary investigator for the purposes of the study outlined in this protocol. The site where the national coordinating investigator is employed is the coordinating site.
The national coordinating investigators are:
Denmark: Lea Kirstine Hansen
Norway: Kirsten Hald
Sweden: Helena Karypidis
Finland: Oskari Heikinheimo
Iceland: Hulda Hjartardóttir
United Kingdom: Andrew Shennan

Site investigators (To be announced)

Each participating site have a site investigator responsible for the conduct of the study on behalf of the site of their employment. At coordinating sites, the national coordinating investigator also acts as site investigator.

Expert Working Groups

Three named working groups have been established: One on laparoscopic cerclage, one on vaginal cerclage, and one on transvaginal ultrasonography. The chairs of the groups have been pointed out as experts in each field contributing with expert knowledge to the development of the protocol and throughout the study period when required.
Chair of the laparoscopic cerclage working group; Pernille Tine Jensen, Denmark.
Chair of the vaginal cerclage working group; Rikke Bek Helmig, Aarhus, Denmark.

Chair of the transvaginal ultrasonography working group; Puk Sandager, Aarhus, Denmark.

6. Introduction

Background

Fifteen million babies worldwide are annually born preterm, and the number is rising [1]. Preterm birth (PTB) is a major cause of neonatal death and serious lifelong disabilities [2]. It is often caused by a dysfunction of the uterine cervix [3]. Normally, the uterine cervix is approximately 35 mm long and composed of strong connective tissue capable of mechanically supporting the growing fetus, the placenta, and the amniotic fluid until the beginning of term labor. A dysfunctional cervix can be weak due to either short length (i.e. after a cervical cone operation) or due to it being composed of weak connective tissue. Pregnant women at risk of PTB may be identified by either history (e.g. prior PTB, late miscarriage, multiple pregnancy), or short cervix (as measured by transvaginal ultrasound scan (TVU)).

A cervical cerclage is a mechanical support to the cervix, where a surgical band or string is applied around the cervix to prevent preterm opening of the dysfunctional cervix, and thereby preventing preterm birth. It can be applied either vaginally or trans-abdominally. The latter can be applied either by laparoscopic or open access surgery.

Vaginal [4] as well as abdominal cerclage [5, 6] can prevent preterm birth, but there is limited evidence as to how to weigh the effectiveness against the disadvantages for each procedure in women with various a priori risk profiles. This uncertainty adds to the variation in use even within the Nordic countries and to The United Kingdom (unpublished data).

In a recent randomized controlled trial (RCT) of women at very high risk of PTB (history of late miscarriage or extreme PTB while treated with vaginal cerclage) [6], 3/39 (8%) of women with an open access abdominal cerclage gave birth before 32 weeks as compared to 11/33 (33%) of women with a low vaginal cerclage and 15/39 (38%) of women with a high vaginal cerclage [6]. These results suggest a significant effect of the open access abdominal to the vaginal procedure.

Advantages of the abdominal cerclage could include a more cranial placement of the cerclage at the cervico-isthmic junction translating into a lower risk of treatment failure. Disadvantages include the need for at least two abdominal surgeries (insertion of cerclage and delivery by cesarean section) including the need for general anesthesia, a possibly redundant procedure if the woman never gets pregnant, and permanency of the cerclage beyond the woman's reproductive period. Very few reports exist of any long-term maternal consequences of a permanent abdominal cerclage suggesting that they are minimal. In comparison to an open procedure, the laparoscopic approach may represent a less invasive procedure with fewer complications [7], but RCTs comparing this technique with the even less traumatic vaginal cerclage have not been performed.

A vaginal cerclage has clear maternal advantages compared to any of the abdominal techniques. The procedure is simpler and can be performed during early pregnancy and in regional anesthesia. Moreover, the cerclage can easily be removed in the third trimester of pregnancy allowing for vaginal delivery.

In year 2022 51 planned vaginal cerclages and 30 laparoscopic abdominal cerclages were undertaken at Aarhus University Hospital.

Other than evidence from the aforementioned trial [6], there is uncertainty if an abdominal cerclage should be preferred over vaginal cerclage, and which women would benefit from it the most.

Moreover, it remains a challenge to establish the PTB risk in the individual woman, as this risk is multifactorial [8], and further to define cut-off risk of at which the abdominal cerclage should be offered. Further, there are considerable differences in obstetric practice internationally, as the abdominal cerclage is not available as treatment in several countries or regions. Finally, there is uncertainty if women are willing to be randomized between a vaginal and laparoscopic cerclage so that an adequately powered trial can be conducted in this anticipated rather small number of eligible participants.
We decided to perform a randomized controlled study with an embedded pilot study to compare vaginal and laparoscopic cerclage in women at moderate to high risk of PTB due to cervical insufficiency. The study is conducted in two stages. The first stage is an embedded pilot study. The purpose of the first stage is to help us investigate the feasibility of the study and make necessary adjustments prior to deciding whether to proceed into the full trial.

7. Study objective

The overall objective for this study is to compare laparoscopic versus vaginal cerclage in women at risk of PTB due to cervical insufficiency.
In the internal pilot study, the objective is to assess the feasibility of the study setup in terms of the recruitment, acceptability of the interventions, the characteristics of included participants, the inclusion rate, the rate of missing data, non-adherence, and other unknown factors or challenges for refinement before proceeding into the full trial.
In the full trial, the objective is to assess the risk of preterm birth before 32 gestational weeks (primary outcome), maternal and neonatal adverse outcomes according to core outcomes in preterm birth [9], and patient preferences.

8. Study design

NORACT is an open, multicentre, superiority randomized controlled study with an embedded internal pilot trial [10-12]. The internal pilot study gives the advantage to use the collected data in the full trial, and is in this setting useful for a number of reasons; the internal pilot is likely to result in minor modifications, we want to test the development of the collaborations, since some sites have limited experience with the tested procedures, and in particular, because of the uncertainties with availability of eligible patients and the ability to recruit [13].

9. Study setting

The study extends from sites in Denmark, The United Kingdom, Sweden, Norway, Finland, and Iceland. Each country will have one or more sites where vaginal and/or laparoscopic cerclages are performed, and so women from all parts of the countries can be referred to these sites for an eligibility evaluation. There will be laparoscopic, vaginal-only study sites (i.e. sites where only a vaginal cerclage can be applied), and recruitment-only sites. In laparoscopic sites, there will be at least one obstetric and one laparoscopic responsible physician investigator.
Data on study sites including the site investigators can be obtained from clinicaltrials.gov.

10. Eligibility criteria

Inclusion criteria

Women in whom the clinician has equipoise as to whether an elective vaginal or abdominal cerclage will be the best intervention to prevent PTB. Examples of women who could be eligible for inclusion are found in Table 1.

Exclusion criteria

Any circumstance under which the clinician is not willing to randomize is an exclusion criterion.
This criterion includes any condition or circumstance under which laparoscopic or vaginal cerclage surgery is contraindicated (i.e. on-going pregnancy of more than 10+0 gestational weeks).
Age <18 years.
Language difficulties.

11. Intervention and comparison

11.1 Intervention: Laparoscopic cerclage

Anesthesia: General.
Timing: Pre-pregnancy.
In unplanned pregnant, but already randomized women, or in women who are identified during pregnancy up till 10+0 weeks of gestation.
Surgical access: Classic or robot-assisted laparoscopy.
Procedure: A manipulator is applied to the non-pregnant uterus according to local routine. Detachment of the bladder peritoneum and bladder, and dissection of the uterine artery are performed at the surgeon's discretion. Non-absorbable woven band or sutures 0-1-2 are used for the cerclage according to local routine.
The cerclage suture is placed in the cervico-corporal angle medial to the uterine arteries. The suture is performed by the Endoclose needle technique [14], an armed suture or band [15, 16]or the Dechamps needle technique [17] with anterior or posterior knots according to local routine. The knot is tied with appropriate tension to fit the suture to the cervical tissue according to the surgeon's discretion.

11.2 Comparison: Vaginal cerclage

Anesthesia: Regional (or general if necessary)
Timing: During pregnancy; from identification of fetal heart rate activity to 16+0 weeks' gestation. The clinician decides whether to wait for normal nuchal translucency scan results before the operation.
Procedure: Ensure viability of the fetus with ultrasound. The needle is passed through the collum substance and mucosa four to eight times and must include enough tissue to withstand the strain of pregnancy. Penetration of the cervical canal is avoided.
Choice of suture material is at the discretion of the surgeon [18].
The suture is placed ad modum McDonald (low) "as high as possible" [19]. If necessary, a Shirodkar (high) procedure is acceptable as an intraoperative decision.
An extra stitch can be placed, if a second stitch can be placed in a more cranial position than the first stitch.

11.3 Common pathway for intervention and comparison arms

Antibiotics: Not recommended in relation to the operation.

Tocolysis: Not recommended in relation to the operation (but not contraindicated if indicated later in pregnancy).
Progesterone: NORACT recommends vaginal Progesterone 200 mg daily from week 16-18 to 34 weeks + 0 days. Local guidelines can be accepted.
Bedrest: Not routinely recommended.
Physical relief and sick leave: To the discretion of the surgeon.
Intercourse: No recommendation against vaginal intercourse.

11.4. Surgical proficiency laparoscopic cerclage

- The NORACT board constitutes a group of proctors, who will conduct the quality assurance on the laparoscopic cerclage procedures.
- The laparoscopic cerclage procedures must be performed by very experienced laparoscopic surgeons
  e.g. consultants experienced with laparoscopic surgery for endometriosis or gynaecologic cancer.
- USS of the cervical length at the 20 week's scan for quality assurance
- Training
  - For laparoscopists experienced in abdominal cerclage procedure: Each laparoscopist will go through one video recording of the cerclage operation with the proctor team.
  - For laparoscopists that have not prior performed this procedure a training session will be arranged:
    - A visit from a proctor or
    - The surgeon visits the proctor or
    - If several needs training we will arrange a workshop hosted by a proctor.
  - The stich-operator may send further video recordings to the proctor group for evaluation and feedback.

11.5 Surgical proficiency vaginal cerclage

- Stich-operators
  - Each site appoints one or two local stich-operators for the study (both vaginal cerclage sites and laparoscopy-sites).
- Stich-site
  - The stich-site may be the laparoscopy-site or at the patient´s local hospital.
  - 1-2 stich-operators per stich-site depending on the number procedures.
- Stich-operators
  - Methods and Training
    - Suture "as high as possible" [19]
    - Pass the needle through collum substance and mucosa four to eight times
    - Must include enough tissue to withstand the strain of pregnancy
    - Avoid penetration of the cervical canal.
    - The stich at the posterior of the cervix is critical. Ensure, that it is applied as high as the stich at the anterior part of the cervix.
    - Tight the suture relatively much to ensure only a narrow cervical canal.

- Extra suture is applied if it can be placed higher up (surgeons discretion).

- USS verification of the cervical length at the 20 week's scan for quality assurance
  - Module: NORACT offers a PROMPT Flex Cervical Cerclage Module (scandidact.dk) training when appropriate.
- Voluntary feedback: The stich-operator may send a PROMPT Flex-cervix with a cerclage to Rikke and Julie for evaluation and feedback.
- Supervision: In case of appointing new stich-operators, a local stich-operator supervises the first 3-5 procedures

12. Outcomes

All outcomes listed below are found in the electronic medical records of the participant and her child. The data is only accessed after verbal and written consent is given. Data from the children's medical records are passed on to the researchers.

Primary clinical outcome of the full trial

There are two prioritized outcomes based on a conditional hierarchical approach in the following order:

1. Delivery <32+0 weeks of gestation (definition: In the first subsequent viable pregnancy (ultrasound detected heart beat) beyond 14+0 weeks of gestation).
2. Baby death (defined as loss of a viable pregnancy beyond 14+0 weeks of gestation, stillbirth, late miscarriage or death of a live born infant within 28 days from date of birth or miscarriage).

Secondary clinical outcomes of the full trial

Maternal outcomes

- Maternal mortality – surgery related.
  - Definition: All deaths of a female within 30 days of the cerclage procedure.
  - Time frame: 30 days after intervention/control
- Maternal mortality
  - Definition: All death of a female of any cause.
  - Time frame: From time of randomisation to 42 days after delivery
- Maternal morbidity – surgery related.
  - Definition: Admission to ICU or a unit that provides 24-h medical supervision and can provide mechanical ventilation or continuous vasoactive drug support within 30 days of the cerclage procedure.
  - Time frame: 30 days after cerclage procedure
- Maternal morbidity – pregnancy related.
  - Definition: Admission to ICU or a unit that provides 24-h medical supervision and can provide mechanical ventilation or continuous vasoactive drug support at any point during pregnancy through 42 days postpartum for pregnancy or childbirth related complications[20]
  - Time frame: From time of randomisation to 42 days after delivery
- Harm to participant – surgery related.
  - Definition:
    - Damage to internal organs (yes/no)

        - Need for re-operation (yes/no)
        - Thromboembolic events (defined as deep vein thrombosis, pulmonary embolism or stroke) (yes/no)
        - Maternal cardiopulmonary arrest (yes/no)
    - Time frame: 30 days after cerclage procedure.
- Harm to participant
    - Definition:
        - Damage to internal organs (yes/no)
        - Need for re-operation (yes/no)
        - Thromboembolic events (defined as deep vein thrombosis, pulmonary embolism or stroke) (yes/no)
        - Maternal cardiopulmonary arrest (yes/no)
    - Time frame: From time of randomisation to 42 days after delivery
- Bleeding – surgery related.
    - Definition: Blood loss ≥500 milliliters
    - Time frame: 30 days after cerclage procedure
- Bleeding – pregnancy related.
    - Definition_ Blood loss ≥ 1000 milliliters
    - Time frame: From time of cerclage procedure to 42 days after delivery
- Maternal infection[9] – surgery related.
    - Definition: Infection leading to antibiotic treatment
    - Time frame: 30 days after cerclage procedure
- Maternal infection[9] – pregnancy related.
    - Definition: Infection leading to antibiotic treatment
    - Time frame: From time of cerclage procedure to 42 days after delivery
- Maternal serious infection[9] – surgery related.
    - Definition: Infection leading to ICU admission
    - Time frame: 30 days after cerclage procedure
- Maternal serious infection[9] – pregnancy related.
    - Definition: Infection leading to ICU admission
    - Time frame: From time of cerclage procedure to 42 days after delivery
- Preterm prelabour rupture of membranes[9]
    - Rupture of membranes before 37 weeks of gestation
    - Time frame: At birth
- Threatened preterm labour
    - Definition: Leading to admission and intervention.
    - Time frame: At birth
- Onset of labour
    - Definition: Spontaneous labor contractions, PROM, induction of labor or c-section.
    - Time frame: At birth
- Mode of birth
    - Definition:
        - Unassisted vaginal

        - Assisted vaginal: Ventouse or forceps
        - C-section: Planned or non-planned
    - Time frame: At birth

Neonatal outcomes

- Modified Neonatal mortality
    - Definition: Death of a liveborn child ≥ 22+0 weeks of gestation
    - Time frame: From birth to four weeks after expected due date
- Neonatal mortality
    - Definition: Death in the 1st 28 days of life ≥ 22+0 weeks of gestation
    - Time frame: 28 days post delivery
- Fetal loss
    - Definition: Composite of late miscarriage (14+0 - 22+0 weeks of gestation) and stillbirth (≥22+0 weeks where baby dies before or during delivery)
    - Timeframe: At expected due date
- Late miscarriage
    - Definition: Delivery between 14+0 – 21+6 weeks of gestation
    - Time frame: At expected due date
- Gestational age at birth[9]
    - Definition: Weeks and days
    - Time frame: At birth
- Preterm birth ≤ 28 weeks
    - Definition: Delivery before ≤ 28 weeks + 0 days
    - Time frame: At birth
- Preterm birth ≤ 34 weeks
    - Definition: Delivery before 34 weeks + 0 days
    - Time frame: At birth
- Preterm birth ≤ 37 weeks
    - Definition: Delivery before 37 weeks + 0 days
    - Time frame: At birth
- Birthweight [9]
    - Definition: Grams
    - Time frame: At birth
- Neonatal admission
    - Definition: Number of consecutive days in hospital within 28 days from delivery. Any admission counts (SCBU, maternity ward, NICU)
    - Time frame: Post delivery
- CNS morbidity[9]
    - Definition:
        - Intraventricular Hemorrhage Grade III and IV (yes/no)
        - Periventricular leukomalacia (yes/no)
    - Time frame: At four weeks after expected due date

- Ocular morbidity
  - Definition: Retinopathy requiring treatment
  - Time frame: At four weeks after expected due date
- Gastrointestinal morbidity[9]
  - Definition: Necrotizing enterocolitits (NEC) requiring surgery (Bells stage 3) and/or spontaneous intestinal perforation (SIP) requiring surgery
  - Time frame: At four weeks after expected due date
- Respiratory support
  - Definition: Mechanical ventilation or non-invasive ventilation (NIV)
  - Time frame: At four weeks after expected due date
- Respiratory Distress Syndrome (RDS)
  - Definition: Surfactant treatment
  - Time frame: 2 days of life
- Early onset infection
  - Definition: ≥5 days of i.v. antibiotics where the treatment starts within the first week after delivery
  - Time frame: At four weeks after expected due date

Internal Pilot study data

The data from the internal pilot study will be descriptive and will report the types and number of participants found eligible for the trial and the feasibility and acceptability of the intervention to inform a decision on whether proceeding with the full RCT is warranted and feasible.

Data:

- Past obstetric history (pregnant and non-pregnant)
  - Definition: Grouped into pre-defined risk groups (table 1) and free text
  - Time frame: 18 months post first recruitment
- Number of participants per country
  - Definition: Number of participants randomised in the trial
  - Time frame: 18 months post first recruitment
- Number of decliners
  - Definition: The number of included women per time and per number of screened (@laparoscopic site) women, in total and in each risk group.
  - Time frame: 18 months post first recruitment
- Adherence to the assigned intervention
  - Definition: See section 20 for definition of adherence.
  - Time frame: 18 months post first recruitment
- Missing data
  - Definition: Data not entered to the data collection instrument
  - Time frame: 18 months post first recruitment
- The feasibility and acceptance of the intervention at sites
  - Definition: Number of enrolled participants per eligible participants and adherence to intervention and time from randomization to procedure

- 18 months post first recruitment

After an 18-month inclusion period, the data monitoring committee will evaluate data from the internal pilot and, based on the pilot study objectives, may recommend to the trial steering committee to change the target population from the broad inclusion criteria to a more specific one, e.g. to one or more pre-specified groups of women (Table 1).
The possible decisions after the pilot study can be 1. Continue with no changes, 2. Continue with limitations to the inclusion criteria (i.e. certain subgroups of women are excluded from the trial), or 3. Not to continue with the full trial. The evaluation will be based on relevant items from the ACCEPT checklist [11].

The trial sites will continue recruitment during the evaluation period of the pilot study.
Further, the NORACT board reserves the right to make smaller, necessary alterations in other logistic or practical aspects of running the trial for the remaining inclusion period.
In case of significant protocol amendments being added to the original protocol, a new version number will be assigned to the protocol. Simultaneously, we will add the amendments to the clinicaltrials.gov registration, and we will submit a supplementary protocol to the Central Denmark Region Committee on Health Research Ethics.

13. Harms and benefits

General considerations

The inherent risks of complications from carrying a child and giving birth exist regardless of the conduct of this trial.
The participants are women who are considered moderate to high risk of late miscarriage or very PTB and would to a large extend be offered one of the two types of interventions regardless of the trial.

Potential harms

The laparoscopic procedure is performed in general anesthesia, the intervention is a permanent placement of a foreign suture material, and the woman can only deliver from a cesarean section. Further, since the operation is performed prior to or in very early pregnancy, there is a risk of the procedure being futile or that the band needs removal (with the operative risks associated herewith) if the woman miscarries at a gestational above 14 weeks or never conceives. There is a small risk of bleeding, harm to adjacent organs and infection.

The vaginal procedure needs to be performed in each pregnancy but otherwise has limited harms. It may prevent PTB to a lower extend in selected groups of women. There is a small risk of pain, bleeding and infection.

Potential benefits

The laparoscopic cerclage may to a higher extend prevent PTB in selected groups of women.
The vaginal cerclage is rarely futile as the operation is performed during pregnancy, it is performed in regional anesthesia, and it is removed by a relatively simple procedure close to term to allow for vaginal delivery.

Potential disadvantages
There may be some geographical inconveniences for the women randomized to the laparoscopic cerclage group, as they may have to travel to a laparoscopic site to have the operation performed. The risk of complications from the two procedures is no different from when the procedures are carried out in the normal clinical handling of the patients but differs slightly as described below.

Adverse event definitions
Adverse event (AE): Any adverse medical occurrence in a trial participant (both maternal and neonatal).
Serious adverse event (SAE): Any untoward and unexpected medical occurrence or effect that:

- Results in maternal, fetal (>22 weeks), or neonatal death
- Is life threatening – refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe
- Requires unexpected hospitalization, or prolongation of existing inpatients' hospitalization
- Results in persistent or significant disability or incapacity

The following are not considered adverse or serious adverse events:

- Admissions or outpatient attendance for common pregnancy conditions e.g.; fetal monitoring, maternal hypertension, antepartum hemorrhage, abdominal pain, non-cephalic presentation, placenta previa
- Admissions or outpatient attendance for common complications from the cerclage procedures e.g.; infections, bleeding from the insertions
- Hospitalization for vaginal cerclage removal, preterm labour, labour, induction of labour, caesarean section, elective treatment for pre-existing conditions
- Admission for common postpartum problems e.g.; maternal hypertension, perineal complications, urinary tract complications, breastfeeding challenges, mental health problems, puerperal infections

Adverse event reporting
All AEs should be recorded. Regarding SAE, an SAE form should be completed by the responsible physician investigator and send to the Principal Investigator and Sponsor within 24 hours from the when the event is known. The SAE form is available in the REDCap database. The REDCap database is constructed in a way, that all above mentioned SAEs will trigger an e-mail alert that is sent to the Trial coordinating investigator and PI. An alert will likewise be triggered once an SAE form has been completed. The SAE will be assessed by the NORACT board and reported to the IDMC individually and at IDMC meetings in summarized form. Assessment of the SAE will be based on available laboratory values and clinical data. If related to any drug administrated as part of the intervention, the summary of product characteristics will be included in the assessment of causality and expectedness of the event.

14. Recruitment

The identification process
Women who meet the inclusion criteria are identified from different pathways.

First, participants are identified at a pre-pregnancy consultation on the management of preventing PTB in a future pregnancy. If the clinician based on anamnesis and/or objective findings deems the woman eligible, she will receive written information on the trial and is referred to one of the laparoscopic sites (if not there already).
In addition to the above, participants could be identified through posters, handouts, and spreads at social media platforms (i.e. facebook groups for women with cerclage, or risk of preterm birth, and hospital instagram accounts) where applicable. If a woman is interested, she can contact a local, corresponding research staff member. If she is possibly eligible, she will receive written information on the trial and is invited to a trial site for further evaluation. Informed consent will be obtained prior to the history and clinical exam.

The screening process
During an already planned, non-research-related, clinical visits, the screening process takes place at a laparoscopic, vaginal-only, or recruitment-only site and consists of the woman's history and the objective examination including a detailed ultrasound evaluation according to pre-specified criteria. Eligible patients will be identified from routine clinical visits and not from screening of medical records. However, data in the medical records from the clinical visits is important to assess the person's eligibility for the trial. No research associated procedures will be undertaken during this process or before consent is obtained.
On the discretion of the responsible investigators, women with conditions that could be associated with increased risks from the surgical procedure are discussed with the laparoscopic surgeons prior to inclusion.

The information process
Regardless of how the woman is identified, the information process is similar for all participants and consists of both written and verbal information.
Written information is handed out on a printed sheet or sent electronically by personal mail in accordance to the preferences of the woman and the circumstances of the identification process.
To secure uniform verbal information, the verbal information is, in each country, centralized to laparoscopic trial sites. When a potential participant is identified and referred, she is booked for a consultation at the nearest laparoscopic site. Verbal information includes information on the background of the trial, inclusion criteria, potential risks and benefits, as well as practical aspects, and purpose of the trial. The verbal information is given by one of the responsible physician investigators or from another assigned research staff member at the laparoscopic site. The woman has the opportunity to request an assessor.
Prior to the beginning of and continuously throughout the enrolment period, members of the local clinical team, the responsible physician investigator, and other assigned research staff members are formally introduced to all aspects of handling the trial.

All eligible women are given time for consideration (an appropriate amount of time is agreed upon individually allowing a minimum of 24 hours if needed), and more time for consideration can be requested. The physician investigator takes responsibility that the eligibility criteria are fulfilled prior to randomisation and obtain written consent. Consent is obtained no later than the time of

randomisation. The consent form is digital, and all signatures are written on a smart phone, a tablet, or a computer using Research Electronic Data Capture (REDCap) which has dedicated functionalities for written consent that are in accordance with the law of data protection.
Consent to participate in this study will give access to data on the participant's health condition, that are needed to conduct the study and to ensure the quality and monitoring that the researchers are obliged to conduct. This data can be obtained by the research responsible, the trial sponsor and his representatives. Furthermore, this data can be accessed by control and monitoring authorities. All data obtained will be assessed in Denmark only and will not be sent to other countries, as this study is anchored in Denmark.

Decliners
Women who decline participation in the trial are asked to sign a separate consent form agreeing to share data on their birthdate, body mass index (BMI), obstetric history (i.e. number, delivery mode, interventions, and gestational age with previous deliveries), previous conization, current clinical findings (cervical length by inspection and ultrasound), their stated reason for declining participating in the trial, and their delivery outcomes. This information is collected for the purpose of assessing the internal validity and the generalizability of the trial and in order to estimate the feasibility of the interventions in eligible women. Second, this data will be presented in the final publication of the results.

15. Sample size
The primary outcome is delivery before 32+0 weeks of gestation. The sample size is based on a target difference of 15% (20% in the vaginal cerclage groups vs. 5% in the abdominal cerclage group). This effect size was estimated based on the rate of delivery before 32+0 weeks of gestation (33% in the vaginal cerclage group vs. 8% in the abdominal cerclage group) in data from Shennan et al.[6]. Since the women included in NORACT are likely to have a somewhat lower risk of PTB compared to the aforementioned study, we assumed a baseline event rate of 20% with the vaginal cerclage and 5% with laparoscopic cerclage (alpha 0.05 and power of 80%). This magnitude of target difference was determined to be important as well as realistic. We inflated for 10% attrition (for those who do not become pregnant, or have an early miscarriage) and a further 10% loss to follow up resulting in a total of 188 women (94 in each group).
For the outcome baby death, the proportions from Shennan et al.[6] were 21% in the vaginal cerclage group versus 3% with laparoscopic cerclage [6]. Again, taking into account the less high risk population in our study and with the sample size of 188 participants, we'd have a power of 80 to detect a target difference of 15%.
Given the uncertainty of the event rate in this less high risk population, it was agreed that the Independent Data and Monitoring Committee (IDMC) would monitor the pooled event rate throughout the study to assess the need to prolong the recruitment period and thereby increase the sample size.

16. Allocation
Eligible women will be identified by the obstetrician during a pre-pregnancy consult. Women will be randomized by a local investigator using an online 24/7 available randomisation software imbedded to REDCap. The women will be randomised in a 1:1 ratio to either laparoscopic or vaginal cerclage with

stratification according to country. The randomisation programme will automatically transfer the entry data to the eCRF in REDCap.

17. Blinding

The trial is open-label.

18. Data collection

All data collection of clinical variables follows the informed consent from the participants.
Data will be collected on electronic standardized forms (eCFR) on which almost every response is pre-coded. The forms are generated using REDCap.
If participants discontinue or their care deviate from the intervention protocols, we will continue to collect data, unless the woman specifically state that we cannot collect or store her data. The responsible investigator or an assigned and educated research staff member from the local clinical team will be responsible for data collection and entry. During the screening process, data* necessary to decide if the patient is eligible for the trial will be entered into REDCap. If the patient decline to participate and do not wish to sign the consent form for decliners or is not found eligible, all registered data will be deleted. The data collected during the screening process, is data that would be obtained for clinical reasons despite this trial and is relevant for the patient's treatment plan outside the trial. All further data will be obtained from the in-hospital electronic medical record after written consent is given. Data from the children's records will be shared within the project.

*The following data will be accessed from the in-hospital electronic medical record aiming to clarify if the potential participant meets the inclusion and exclusion criteria:

- Unique patient identifier (Danish Central Personal Register number)
- Patient name
- Length of cervix
- Body mass index
- Smoking (yes/no)
- Information on:
    - Parity
    - Prior caesarean delivery
    - Cervical surgery (conizations)
    - Previous preterm birth
    - Previous late miscarriages

Variables

A detailed data dictionary that clearly defines all included variables was created prior to patient enrolment. The data dictionary provides the name of the variable (including the code used in the database), a detailed definition of the variable, categories for categorical variables, and units and ranges for continuous variables. The data dictionary is available at the trial website (www.noract.dk).

Maternal characteristics at time of randomisation

These data are found in the participants' electronic medical records

- Maternal age (years)
- Parity (numerical)
- Body mass index (BMI) (kg/m2)
- Smoking (current smoker at time of randomisation (yes/no)
- Country of residence

Maternal risk factors for preterm birth

- Prior caesarean delivery (CS) (yes/no)
    - Planned CS
    - Non-planned prior to labor
    - Non-planned CS during 1st stage of labour (CS between 4-9 cm dilatation)
    - Non-planned CS during 2nd stage of labour (Full dilatation)
- Prior cervical conization (yes/no)
    - If yes; Number of prior cervical conizations (no.)
- Congenital uterine malformation
    - Dideplhus, septum, arcuate uterus
- Obstetrical history in each prior pregnancy beyond 14 weeks of gestation.
    - Pregnancy number
    - Maternal age (years)
    - Singleton or multiple gestation
    - Failed elective vaginal cerclage (yes/no)
    - Failed USS indicated cerclage (yes/no)
    - Gestational age at pregnancy ending (weeks and days)
    - Miscarriage (yes/no)
        - If yes; spontaneous or induced and reason for induced if yes.
    - Onset of labour
        - Spontaneous labor contractions
        - PPROM
        - PROM
        - Induction of labour
        - C-section
- Mode of birth
    - Unassisted vaginal delivery
    - Asssisted vaginal (forceps or ventouse)
    - Planned caesarean section
    - Non-planned caesarean section before labor
    - Non-planned CS during 1st stage of labour(CS between 4-9 cm dilatation)
    - Non-planned CS during 2nd stage of labour (full dilatation)

Characteristics of the surgical procedure

These data are found in the participants' electronic medical records and are used for analyses for outcomes:

- Type of cerclage procedure
  - Vaginal purse string with bladder mobilisation
  - Vaginal purse string without bladder mobilisation
  - Laparoscopic cerclage
- Timing of the procedure (before conception/in early pregnancy)
  - If in pregnancy; gestational age at cerclage placement
- Anaesthesia (general/regional)
- Surgeons experience, years
- Time in hospital (days)
- Transvaginal ultrasonography documentation after the cerclage placement (within 14 days)
- Blood loss (milliliters)
- If laparoscopic cerclage;
  - Number of ports
  - Manipulator is applied to the uterus (yes/no)
  - Cerclage material (multifilament/monofilament)
  - Placement of knot(s) (anterior/posterior)
  - Administration of antibiotics (yes/no)
  - Additional procedures performed during surgery (e.g. hysteroscopy, removal of endometriosis
- If vaginal cerclage;
  - Number of sutures (1/2)
  - Type of suture
  - Administration of antibiotics (yes/no)
  - PPROM (yes/no)

Characteristics of the 'NORACT' pregnancy (the first viable pregnancy beyond 14 weeks following randomisation)
These data are found in the participants' electronic medical records and are used for analyses for outcomes:

- Maternal age (years)
- Parity (numerical)
- Mode of conception
  - Spontaneous
  - Assisted reproductive therapy (ART)
- Ultrasound determined due date or best determined GA from best practise at site
- Singleton or multiple gestation
- Rescue cerclage (yes/no)
- Treatment with vaginal progesterone (yes/no)
  - If yes; from which gestational week

- Administration of lung maturation (betamethasone) <34 weeks of gestation (yes/no)
- Administration of tocolytics <34 weeks of gestation (yes/no)
- Treatment with antibiotics (yes/no)
    - If yes; which indication (PPROM, short cervix, other infection)
    - If yes; at which gestational age
- Onset of labour (spontaneous labor contractions, induction of labour, C-section, PROM)
- Mode of birth (vaginal, assisted vaginal, caesarean)

19. Data management

All outcome data will be registered in an eCRF designed for the trial using the REDCap database. Study data will be collected and managed using REDCap electronic data capture tools hosted at Aarhus University, Denmark [21]. REDCap is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.

Data will be handled according to national laws on data protection (in Denmark including the General Data Protection Regulation and the Data Protection Act). In Denmark, the project is registered with the Central Denmark Region's internal list of research projects. Data will be used for the purpose outlined in this trial protocol.

20. Adherence

We have defined adherence as those participants in the vaginal cerclage group who receives a vaginal cerclage before 16+0 weeks of pregnancy and those participants in the laparoscopic cerclage group who receives a laparoscopic cerclage before 10+0 weeks of pregnancy. Subsequent exam-indicated vaginal cerclage in either group will count as adherent.

21. Analyses

All estimates of differences between groups will be presented with two-sided 95% confidence intervals, unless otherwise stated. For the primary outcome of preterm birth, a p-value will be produced, with statistical significance considered at the 5% level.

For the second prioritized primary outcome of baby death, we will incorporate a conditional hierarchical approach to hypothesis testing to ensure we appropriately control for the overall rate of type I error(5). If the primary outcome of preterm birth meets a superiority conclusion in favour of either a vaginal or laparoscopic cerclage, we will then proceed to examine any differences between the two procedures for baby death. If the p-value from this test (baby death) is less than or equal to 0.05 in the model (or if the 95% confidence interval does not contain one) we will declare superiority for this outcome.

Other secondary outcomes will be considered as exploratory; no adjustment for multiple comparisons will be made and hence significance should not be inferred from the confidence interval width.

All primary analyses (primary and secondary outcomes) will be conducted on a modified intention-to-treat basis only including patients who are pregnant at time of randomisation or become pregnant

after randomisation and carry a pregnancy beyond 14+0 weeks. Participants who have an early miscarriage will be excluded post randomisation, unless they have a viable pregnancy beyond 14+0 weeks later in the study period. The rationale behind this decision is, that an early miscarriage is unlikely to be caused by an incompetent cervix. Participants will be analysed in the intervention group to which they were randomised, and all participants shall be included whether or not they received the allocated intervention.

A secondary per protocol and as-treated analysis will be performed for each treatment group for the primary outcomes only (see section 20 for description of whom will perform the per protocol analysis).

Presentation of the quantitative data from the internal pilot will largely consist of descriptive statistics and comparisons between the two groups. The inclusion number will be described according to country, site, and groups in Table 1. The reasons for ineligibility, refusal, loss to follow-up, or missing data will be categorised and described as overall frequencies per country, site, and according to groups in Table 1. No outcome data will be available for evaluation.

Subgroup analyses will be conducted to determine whether there are signs of an effect for each pre-specified subgroups. To ensure validity to the subgroup analysis, the factors considered for subgroup analyses is pre-specified below:

- Participants with a history of emergency/laboring caesarean section followed by a spontaneous singleton late miscarriage or preterm birth 14+0-28+0 weeks.
- Participants with a prior elective vaginal cerclage placement but nonetheless a spontaneous late miscarriage or PTB between 14+0 and 28+0* weeks
- History of a prior emergency cerclage with delivery between 14+0 and 28+0* weeks
- Participants with a history of one or more deliveries between gestational age 16+0 to 28 +0 and a clinical diagnosis of cervical insufficiency.
- Any conization and a short pre-pregnancy cervix (e.g. short ectocervix with inspection or below 15-20 mm with ultrasound)
- History of three or more deliveries GA 16+0 to 36+6 weeks

The statistical analyses and reporting will adhere to the Consolidated Standards of Reporting Trials (CONSORT)-guidelines[23, 24].
STATA and 'R' will be used for data management and analyses.

Patient inclusion and exclusion will be illustrated in a modified CONSORT flow diagram for non-pharmacologic trials[25] (see figure 1).

See the full analysis plan for further details.

22. Monitoring and oversight

The trial is monitored according to Good Clinical Practice (GCP) standards.
A decision as to perform an interim analysis will made after the internal pilot period. The data monitoring committee will evaluate pilot data as described above presented by the PI at the ending of the internal pilot after 18 months of inclusion.

In the full trial, there will be no predefined stopping criteria, and criteria for termination will be at the discretion of the trial steering committee and the Trial Sponsor.

Three independent members have been appointed to a Trial Steering Committee (TSC) prior to commencement.
The role of the TSC is to provide independent overall supervision for the trial on behalf of the NORACT board including advice on

- Protocol elaboration
- Problems occurring during the study
- Interpretation of the results

Three independent members have been appointed to the Independent Data Monitoring Committee (IDMC) prior to commencement.

- The IDMC members are to safeguard the interests of trial participants, assess the safety of the intervention during the trial, and monitor the overall conduct of the clinical trial.
- The NORACT board will review de-identified data for safety at predetermined milestones (approximately halfway through the inclusion) but can – at any time – require extra reviews. After the reviews, the IDMC will create a short report to the TSC with recommendations for continuation, modifications, or termination of the trial.

Charters describing the roles and responsibilities of the IDMC and the TSC, including the timings of meetings, methods of providing information between the IDMC and the TSC, frequency and format of meetings, statistical issues and relationships with other committees have been approved and signed. See appendix 1 for the signed declarations.

23. Ethics and dissemination

The study will be conducted in accordance with the ethical principles outlined in the latest version of the 'Declaration of Helsinki' and the 'Guideline for Good Clinical Practice' related to experiments on humans. Approval of the study will be sought from the Central Denmark Region Committees on Health Research Ethics. The results of the study will be reported according to the CONSORT 2010 statement.
Any possible risks associated with the conduct of the trial are not, neither on their own nor compared to the expected gain from the trial, expected to reach an indefensible extent. The therapeutic and public health gain of the trial is expected to justify the trial. The sake of the trial participants will at any time override the sake of the conduct of the trial. The results of this trial have the potential to generate important knowledge for the improvement of PTB and the potentially lower the mortality and morbidity caused by PTB in future high risk pregnancies.

24. Patient and public involvement

Prior to the NORACT study, we will perform a qualitative study in women with vaginal and laparoscopic cerclages on their experience, information, and preference for a cerclage. An individual protocol for this study will be drafted.
We will seek to form a formal patient representative group with members from at least two countries to participate in the management of the study, the information distributed to eligible participants, and the dissemination of the results.

25. Declaration of interests

None of the protocol authors has conflicts of interest to declare.

26. Publication

Positive, inconclusive as well as negative results from the trial will be published in peer reviewed international scientific journals. The trial coordinating investigator will draft these papers as first author, and principal investigator Julie Glavind will be last corresponding author. Additional authorship will follow standard authorship guidelines and will include all members of the NORACT board and the representatives from the secondary and tertiary trial sites according to a prespecified list of types of engagement.

27. Access to data

After publication of the trial results, the final dataset will be publicly available in an anonymized form using i.e. Zenodo open data repository (CERN) or another equivalent database.

28. Ancillary and post-trial care

In Denmark, participants taking part in clinical studies are insured during and after the trial according to the Act on Patient Safety in the Danish Health Care System.

29. Abbreviations

ART – Assisted reproductive therapy
BMI – Body mass index
CNS – Central Nervous System
CS – Caesarean section
eCRF – electronic Case Record Form
FDCS – Full dilatation caesarean section
GA – gestational age
GCP – Good Clinical Practice
GDPR – General Data Protection Regulation
IDMC – Independent Data Monitoring Committee
NICU – Neonatal intensive care unit
PPROM – Preterm prelabor rupture of membranes
PROM – Prelabor rupture of membranes
PTB – Preterm birth
RCT – Randomised Controlled trial
REDCap - Research Electronic Data Capture
RR – Relative Risk
SCBU – Special care baby unit
TSC – Trial Steering Committee
TVU – Transvaginal ultrasound
USS – Ultra sound scan

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Tables and figures

Table 1. Categories of women for data-analysis. These groups are examples of women who could participate in the study. Pilot study inclusion criteria: Women in whom the clinician has equipoise as to whether an elective vaginal or abdominal cerclage will be the best treatment to prevent PTB.
History of emergency/laboring cesarean section followed by a spontaneous singleton late miscarriage or PTB from 14+0 to 28+0* weeks
History with a prior elective vaginal cerclage placement but nonetheless a spontaneous late miscarriage or PTB between 14+0 and 28+0* weeks
History of a prior emergency cerclage with delivery between 14+0 and 28+0* weeks
Any conization and a short pre-pregnancy cervix (e.g. short ectocervix with inspection or below 15-20 mm with ultrasound)
History of one or more deliveries GA 16+0 to 28+0 weeks and a clinical diagnosis of cervical insufficiency
History of three or more deliveries GA 16+0 to 36+6 weeks
Others

* Women with delivery up to 32 weeks might be considered depending on a clinical judgement

Figure 1, CONSORT diagram

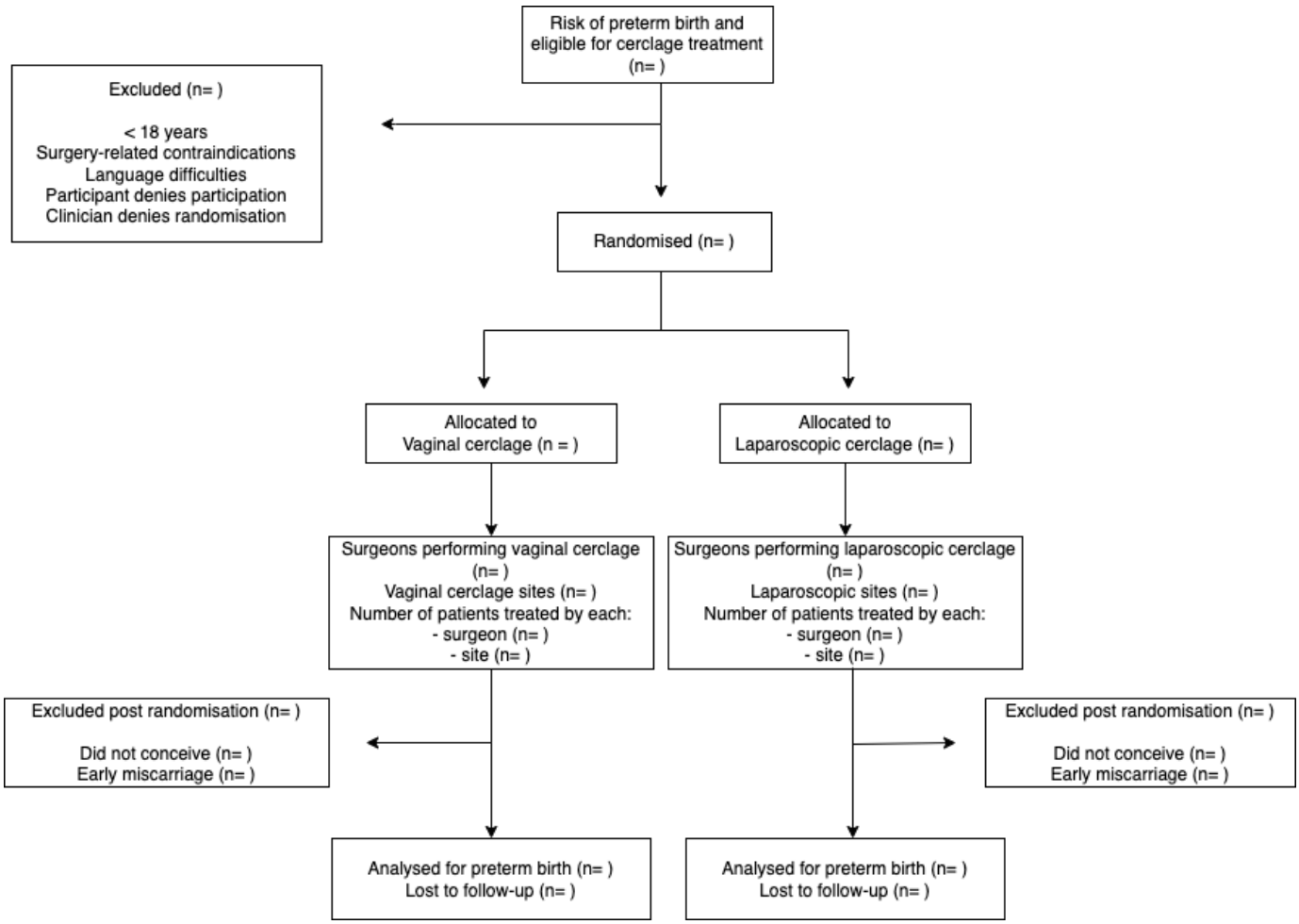


Figure 2, Participant flow through the trial

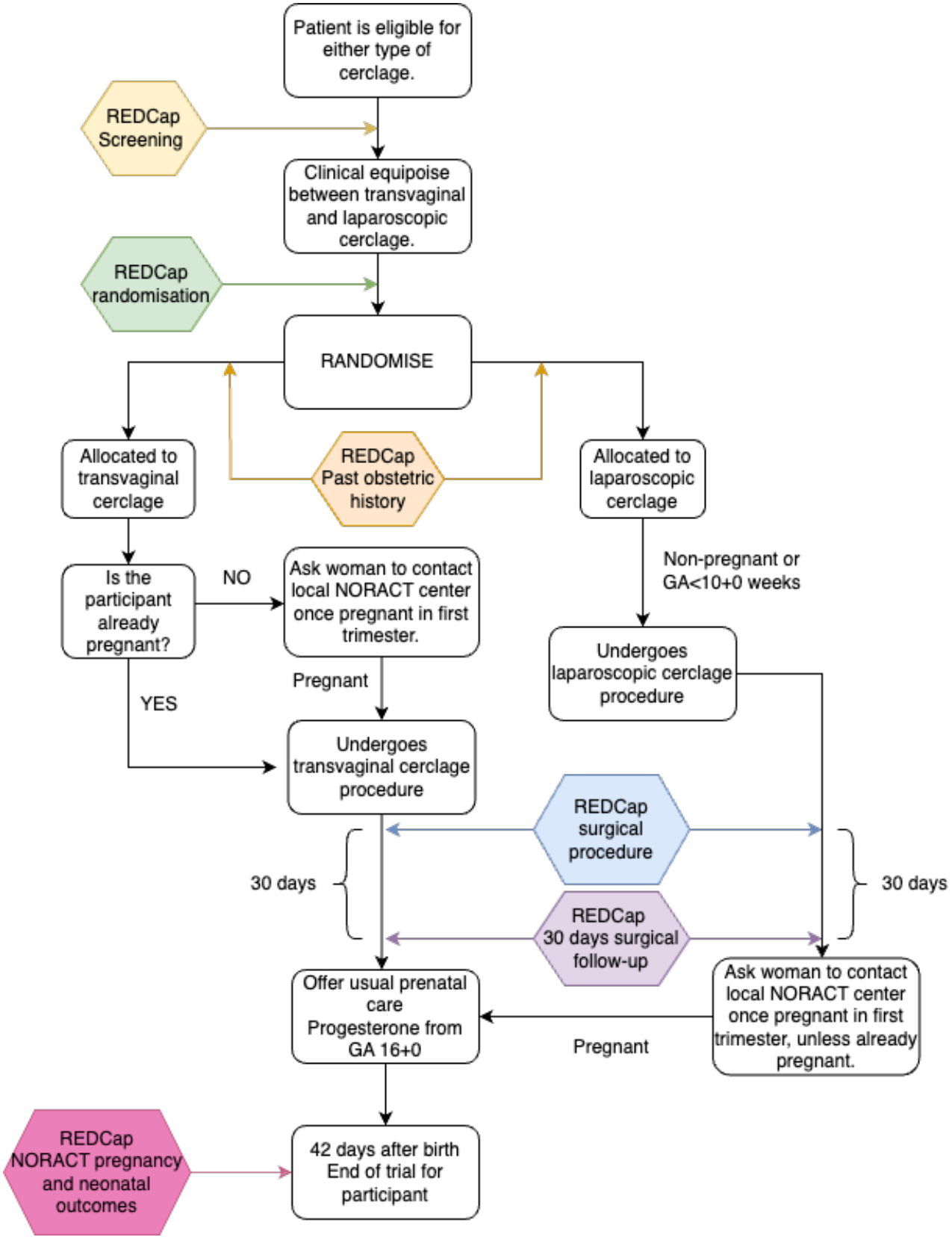
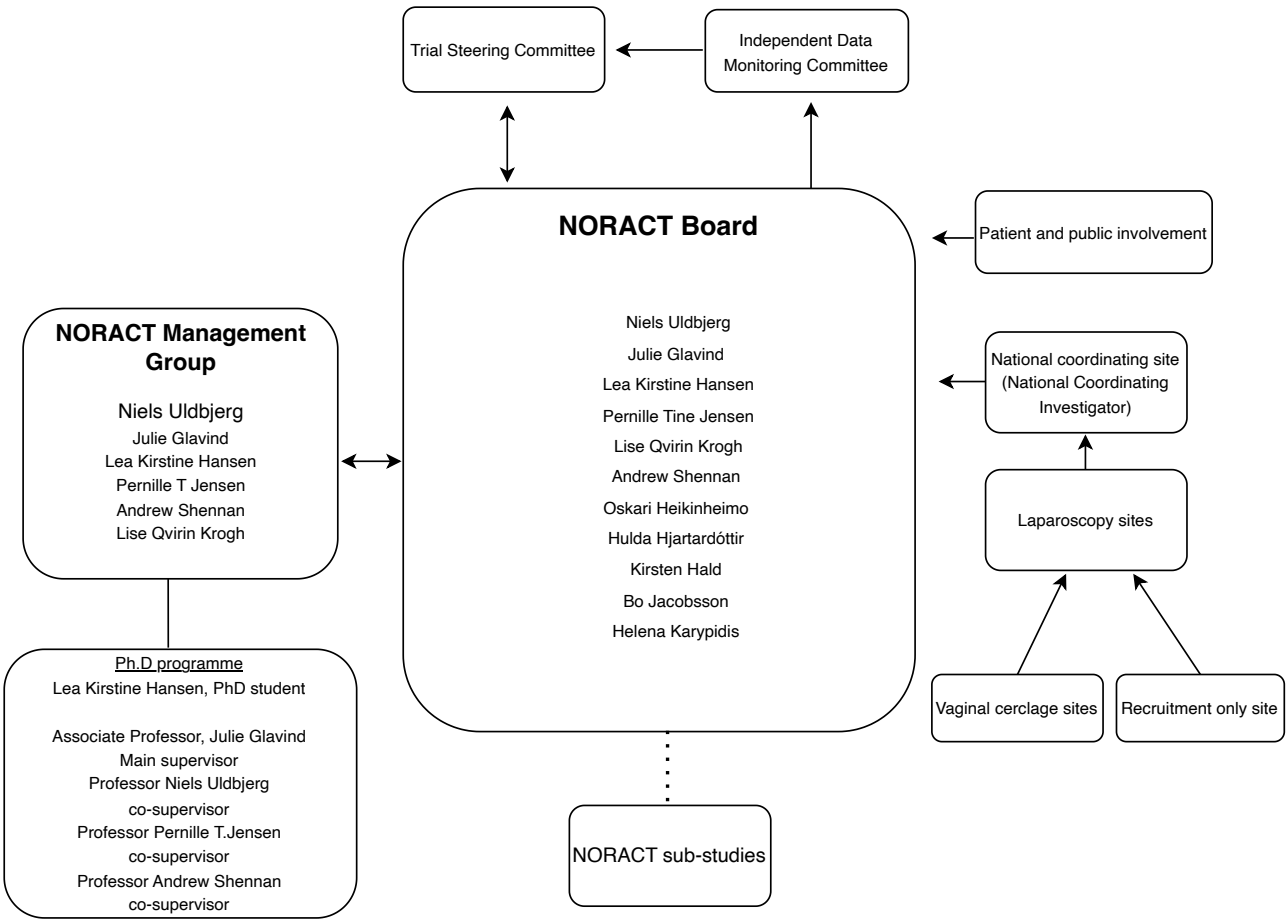
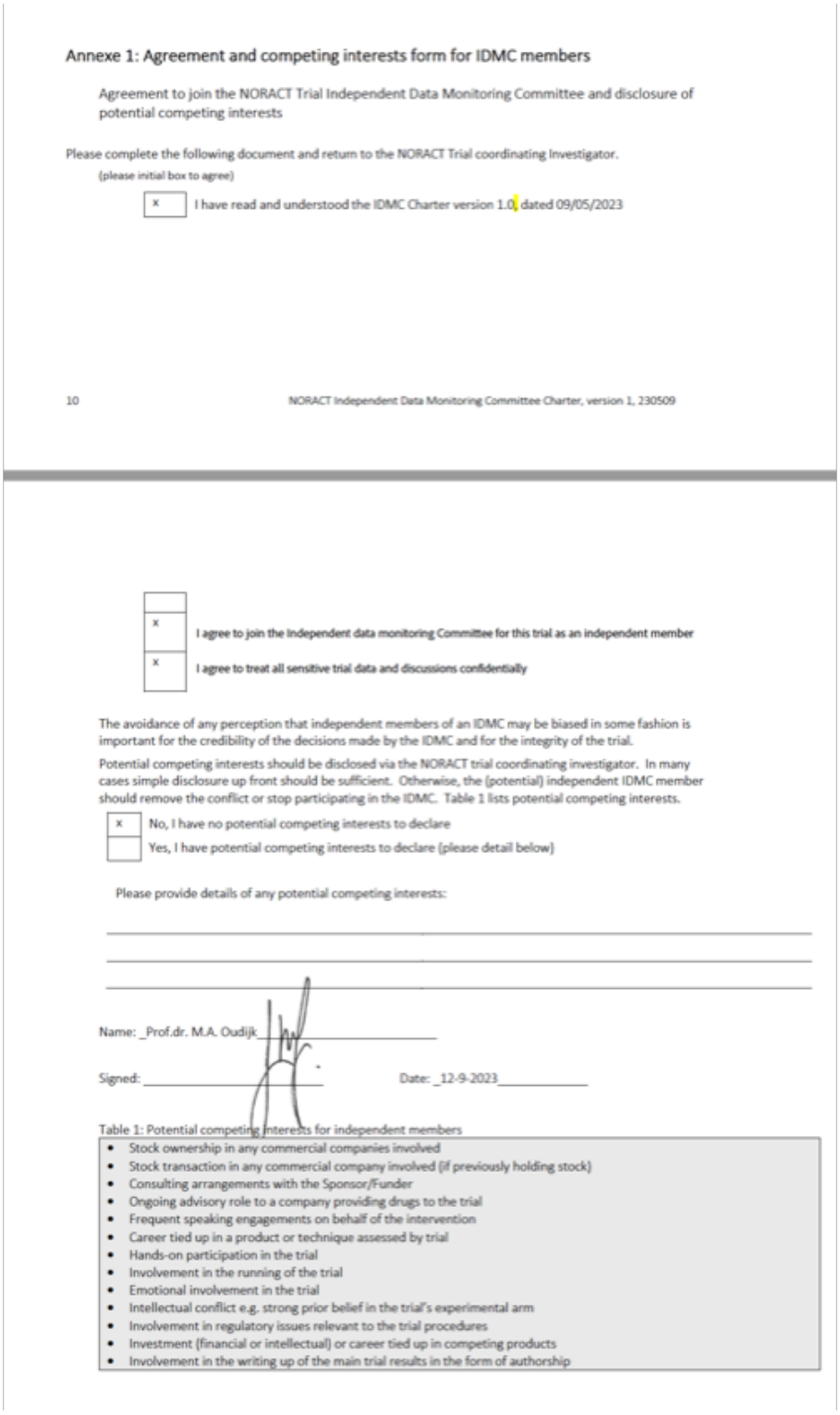


Figure 3, Organization of the trial


Trial Steering Committee
Independent Data Monitoring Committee
NORACT Board
Niels Uldbjerg
Julie Glavind
Lea Kirstine Hansen
Pernille Tine Jensen
Lise Qvirin Krogh
Andrew Shennan
Oskari Heikinheimo
Hulda Hjartardóttir
Kirsten Hald
Bo Jacobsson
Helena Karypidis
Patient and public involvement
National coordinating site (National Coordinating Investigator)
Laparoscopy sites
Vaginal cerclage sites
Recruitment only site
NORACT Management Group
Niels Uldbjerg
Julie Glavind
Lea Kirstine Hansen
Pernille T Jensen
Andrew Shennan
Lise Qvirin Krogh
Ph.D programme
Lea Kirstine Hansen, PhD student
Associate Professor, Julie Glavind
Main supervisor
Professor Niels Uldbjerg
co-supervisor
Professor Pernille T.Jensen
co-supervisor
Professor Andrew Shennan
co-supervisor
NORACT sub-studies

Appendix 1.

Signed declarations from TSC and IDMC members.



Annexe 1: Agreement and competing interests form for IDMC members

Agreement to join the NORACT Trial Independent Data Monitoring Committee and disclosure of potential competing interests

Please complete the following document and return to the NORACT Trial coordinating Investigator.

(please initial box to agree)

[x] I have read and understood the IDMC Charter version 1.0, dated 09/05/2023

10 NORACT Independent Data Monitoring Committee Charter, version 1, 230509

[ ]
[x] I agree to join the Independent data monitoring Committee for this trial as an independent member
[x] I agree to treat all sensitive trial data and discussions confidentially

The avoidance of any perception that independent members of an IDMC may be biased in some fashion is important for the credibility of the decisions made by the IDMC and for the integrity of the trial.

Potential competing interests should be disclosed via the NORACT trial coordinating investigator. In many cases simple disclosure up front should be sufficient. Otherwise, the (potential) independent IDMC member should remove the conflict or stop participating in the IDMC. Table 1 lists potential competing interests.

[x] No, I have no potential competing interests to declare
[ ] Yes, I have potential competing interests to declare (please detail below)

Please provide details of any potential competing interests:

Name: _Prof.dr. M.A. Oudijk_____

Signed: _____ Date: _12-9-2023_____

Table 1: Potential competing interests for independent members

- Stock ownership in any commercial companies involved
- Stock transaction in any commercial company involved (if previously holding stock)
- Consulting arrangements with the Sponsor/Funder
- Ongoing advisory role to a company providing drugs to the trial
- Frequent speaking engagements on behalf of the intervention
- Career tied up in a product or technique assessed by trial
- Hands-on participation in the trial
- Involvement in the running of the trial
- Emotional involvement in the trial
- Intellectual conflict e.g. strong prior belief in the trial's experimental arm
- Involvement in regulatory issues relevant to the trial procedures
- Investment (financial or intellectual) or career tied up in competing products
- Involvement in the writing up of the main trial results in the form of authorship

Annexe 1: Agreement and competing interests form for IDMC members

Agreement to join the NORACT Trial Independent Data Monitoring Committee and disclosure of potential competing interests

Please complete the following document and return to the NORACT Trial coordinating investigator.

(please initial box to agree)

- [x] I have read and understood the IDMC Charter version xxx, dated 1.00 9/5/2023
- [x] I agree to join the Data Monitoring Committee for this trial as an independent member
- [x] I agree to treat all sensitive trial data and discussions confidentially

The avoidance of any perception that independent members of an IDMC may be biased in some fashion is important for the credibility of the decisions made by the IDMC and for the integrity of the trial.

Potential competing interests should be disclosed via the NORACT trial coordinating investigator. In many cases simple disclosure up front should be sufficient. Otherwise, the (potential) independent IDMC member should remove the conflict or stop participating in the IDMC. Table 1 lists potential competing interests.

- [x] No, I have no potential competing interests to declare
- [ ] Yes, I have potential competing interests to declare (please detail below)

Please provide details of any potential competing interests:

Name: Paul T. Seed

Signed: Paul Seed Date: 18 Sept 2023

Table 1: Potential competing interests for independent members

- Stock ownership in any commercial companies involved
- Stock transaction in any commercial company involved (if previously holding stock)
- Consulting arrangements with the Sponsor/Funder
- Ongoing advisory role to a company providing drugs to the trial
- Frequent speaking engagements on behalf of the intervention
- Career tied up in a product or technique assessed by trial
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- Involvement in regulatory issues relevant to the trial procedures
- Investment (financial or intellectual) or career tied up in competing products
- Involvement in the writing up of the main trial results in the form of authorship

Annexe 1: Agreement and competing interests form for IDMC members

Agreement to join the NORACT Trial Independent Data Monitoring Committee and disclosure of potential competing interests

Please complete the following document and return to the NORACT Trial coordinating Investigator.

(please initial box to agree)

x	I have read and understood the IDMC Charter version 1 , dated 09/05/2023
x	I agree to join the Data Monitoring Committee for this trial as an independent member
x	I agree to treat all sensitive trial data and discussions confidentially

The avoidance of any perception that independent members of an IDMC may be biased in some fashion is important for the credibility of the decisions made by the IDMC and for the integrity of the trial.

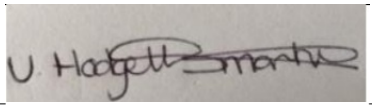
Potential competing interests should be disclosed via the NORACT trial coordinating investigator. In many cases simple disclosure up front should be sufficient. Otherwise, the (potential) independent IDMC member should remove the conflict or stop participating in the IDMC. Table 1 lists potential competing interests.

x	No, I have no potential competing interests to declare
	Yes, I have potential competing interests to declare (please detail below)

Please provide details of any potential competing interests: _____

_____

Name: _____Vicky Hodgetts Morton_____

Signed: _____  _____

Date: _____06/10/2023_____

Table 1: Potential competing interests for independent members

- Stock ownership in any commercial companies involved
- Stock transaction in any commercial company involved (if previously holding stock)
- Consulting arrangements with the Sponsor/Funder
- Ongoing advisory role to a company providing drugs to the trial
- Frequent speaking engagements on behalf of the intervention
- Career tied up in a product or technique assessed by trial
- Hands-on participation in the trial
- Involvement in the running of the trial
- Emotional involvement in the trial
- Intellectual conflict e.g. strong prior belief in the trial's experimental arm
- Involvement in regulatory issues relevant to the trial procedures
- Investment (financial or intellectual) or career tied up in competing products
- Involvement in the writing up of the main trial results in the form of authorship

Annexe 1: Agreement and competing interests form for independent members

Agreement to join the NORACT Trial Steering Committee as an independent member and disclosure of potential competing interests

Please complete the following document and return to the NORACT Trial coordinating Investigator.

(please initial box to agree)

x	I have read and understood the TSC Charter version 1,0, dated 13/06/2023
x	I agree to join the Trial Steering Committee for this trial as an independent member
x	I agree to treat all sensitive trial data and discussions confidentially

The avoidance of any perception that independent members of a TSC may be biased in some fashion is important for the credibility of the decisions made by the TSC and for the integrity of the trial.

Potential competing interests should be disclosed via the NORACT trial coordinating investigator. In many cases simple disclosure up front should be sufficient. Otherwise, the (potential) independent TSC member should remove the conflict or stop participating in the TSC. Table 1 lists potential competing interests.

x	No, I have no potential competing interests to declare
	Yes, I have potential competing interests to declare (please detail below)

Please provide details of any potential competing interests:

Name: __Nigel Simpson__

Signed: __ __ Date: _____30/8/23_____

Table 1: Potential competing interests for independent members

- Stock ownership in any commercial companies involved
- Stock transaction in any commercial company involved (if previously holding stock)
- Consulting arrangements with the Sponsor/Funder
- Ongoing advisory role to a company providing drugs to the trial
- Frequent speaking engagements on behalf of the intervention
- Career tied up in a product or technique assessed by trial
- Hands-on participation in the trial
- Involvement in the running of the trial
- Emotional involvement in the trial
- Intellectual conflict e.g. strong prior belief in the trial's experimental arm
- Involvement in regulatory issues relevant to the trial procedures
- Investment (financial or intellectual) or career tied up in competing products
- Involvement in the writing up of the main trial results in the form of authorship

Annexe 1: Agreement and competing interests form for independent members

Agreement to join the NORACT Trial Steering Committee as an independent member and disclosure of potential competing interests

Please complete the following document and return to the NORACT Trial coordinating Investigator.

(please initial box to agree)

x	I have read and understood the TSC Charter version 1,0, dated 13/06/2023
x	I agree to join the Trial Steering Committee for this trial as an independent member
x	I agree to treat all sensitive trial data and discussions confidentially

The avoidance of any perception that independent members of a TSC may be biased in some fashion is important for the credibility of the decisions made by the TSC and for the integrity of the trial.

Potential competing interests should be disclosed via the NORACT trial coordinating investigator. In many cases simple disclosure up front should be sufficient. Otherwise, the (potential) independent TSC member should remove the conflict or stop participating in the TSC. Table 1 lists potential competing interests.

x	No, I have no potential competing interests to declare
	Yes, I have potential competing interests to declare (please detail below)

Please provide details of any potential competing interests:

_____

_____

_____

Name: _____Caroline Fox_____

Signed: _____ _____ Date: ____8.9.23____

Table 1: Potential competing interests for independent members

- Stock ownership in any commercial companies involved
- Stock transaction in any commercial company involved (if previously holding stock)
- Consulting arrangements with the Sponsor/Funder
- Ongoing advisory role to a company providing drugs to the trial
- Frequent speaking engagements on behalf of the intervention
- Career tied up in a product or technique assessed by trial
- Hands-on participation in the trial
- Involvement in the running of the trial
- Emotional involvement in the trial
- Intellectual conflict e.g. strong prior belief in the trial's experimental arm
- Involvement in regulatory issues relevant to the trial procedures
- Investment (financial or intellectual) or career tied up in competing products
- Involvement in the writing up of the main trial results in the form of authorship

Annexe 1: Agreement and competing interests form for independent members

Agreement to join the NORACT Trial Steering Committee as an independent member and disclosure of potential competing interests

Please complete the following document and return to the NORACT Trial coordinating investigator.

(please initial box to agree)

CM	I have read and understood the TSC Charter version 1.0, dated 13/06/2023
CM	I agree to join the Trial Steering Committee for this trial as an independent member
CM	I agree to treat all sensitive trial data and discussions confidentially

The avoidance of any perception that independent members of a TSC may be biased in some fashion is important for the credibility of the decisions made by the TSC and for the integrity of the trial.

Potential competing interests should be disclosed via the NORACT trial coordinating investigator. In many cases simple disclosure up front should be sufficient. Otherwise, the (potential) independent TSC member should remove the conflict or stop participating in the TSC. Table 1 lists potential competing interests.

CM	No, I have no potential competing interests to declare
	Yes, I have potential competing interests to declare (please detail below)

Please provide details of any potential competing interests:

_____

_____

_____

Name: Catherine Moakes

Signed: C A MOAKES Date: 16/09/2023

Table 1: Potential competing interests for independent members

- Stock ownership in any commercial companies involved
- Stock transaction in any commercial company involved (if previously holding stock)
- Consulting arrangements with the Sponsor/Funder
- Ongoing advisory role to a company providing drugs to the trial
- Frequent speaking engagements on behalf of the intervention
- Career tied up in a product or technique assessed by trial
- Hands-on participation in the trial
- Involvement in the running of the trial
- Emotional involvement in the trial
- Intellectual conflict e.g. strong prior belief in the trial's experimental arm
- Involvement in regulatory issues relevant to the trial procedures
- Investment (financial or intellectual) or career tied up in competing products
- Involvement in the writing up of the main trial results in the form of authorship

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Annexe 2: Agreement and competing interests form for non-independent members

Agreement to join the NORACT Trial Steering Committee as a non-independent member and disclosure of potential competing interests

Please complete the following document and return to the NORACT Trial coordinating Investigator.

(please initial box to agree)

X	I have read and understood the TSC Charter version 1,0 dated 13/06/2023
X	I agree to join the Trial Steering Committee for this trial as a non-independent member
X	I agree to treat all sensitive trial data and discussions confidentially

The avoidance of any perception that non-independent members of a TSC may be biased in some fashion is important for the credibility of the decisions made by the TSC and for the integrity of the trial.

Potential competing interests should be disclosed via the NORACT trial coordinating investigator. In many cases simple disclosure up front should be sufficient. Otherwise, the (potential) independent TSC member should remove the conflict or stop participating in the TSC. Table 1 lists potential competing interests.

	No, I have no potential competing interests to declare
X	Yes, I have potential competing interests to declare (please detail below)

Please provide details of any potential competing interests:

Supervisor to Lea Kirstine Hansen

Name: _____Julie Glavind_____

Signed: Julie Glavind Date: _____8/9-23_____

Table 1: Potential competing interests for non-independent members

- Stock ownership in any commercial companies involved
- Stock transaction in any commercial company involved (if previously holding stock)
- Consulting arrangements with the Sponsor/Funder
- Ongoing advisory role to a company providing drugs to the trial
- Frequent speaking engagements on behalf of the intervention
- Career tied up in a product or technique assessed by trial
- Hands-on participation in the trial
- Involvement in the running of the trial
- Emotional involvement in the trial
- Intellectual conflict e.g. strong prior belief in the trial's experimental arm
- Involvement in regulatory issues relevant to the trial procedures
- Investment (financial or intellectual) or career tied up in competing products

Annexe 2: Agreement and competing interests form for non-independent members

Agreement to join the NORACT Trial Steering Committee as a non-independent member and disclosure of potential competing interests

Please complete the following document and return to the NORACT Trial coordinating Investigator.

(please initial box to agree)

X	I have read and understood the TSC Charter version 1,0 dated 13/06/2023
X	I agree to join the Trial Steering Committee for this trial as a non-independent member
X	I agree to treat all sensitive trial data and discussions confidentially

The avoidance of any perception that non-independent members of a TSC may be biased in some fashion is important for the credibility of the decisions made by the TSC and for the integrity of the trial.

Potential competing interests should be disclosed via the NORACT trial coordinating investigator. In many cases simple disclosure up front should be sufficient. Otherwise, the (potential) independent TSC member should remove the conflict or stop participating in the TSC. Table 1 lists potential competing interests.

X	No, I have no potential competing interests to declare
	Yes, I have potential competing interests to declare (please detail below)

Please provide details of any potential competing interests:

_____

_____

_____

Name: ____Lea Kirstine Hansen

Signed:  Date: ____12/9-2023_____

Table 1: Potential competing interests for non-independent members

- Stock ownership in any commercial companies involved
- Stock transaction in any commercial company involved (if previously holding stock)
- Consulting arrangements with the Sponsor/Funder
- Ongoing advisory role to a company providing drugs to the trial
- Frequent speaking engagements on behalf of the intervention
- Career tied up in a product or technique assessed by trial
- Hands-on participation in the trial
- Involvement in the running of the trial
- Emotional involvement in the trial
- Intellectual conflict e.g. strong prior belief in the trial's experimental arm
- Involvement in regulatory issues relevant to the trial procedures
- Investment (financial or intellectual) or career tied up in competing products

Annexe 2: Agreement and competing interests form for non-independent members

Agreement to join the NORACT Trial Steering Committee as a non-independent member and disclosure of potential competing interests

Please complete the following document and return to the NORACT Trial coordinating Investigator.

(please initial box to agree)

x	I have read and understood the TSC Charter version 1,0 dated 13/06/2023
x	I agree to join the Trial Steering Committee for this trial as a non-independent member
x	I agree to treat all sensitive trial data and discussions confidentially

The avoidance of any perception that non-independent members of a TSC may be biased in some fashion is important for the credibility of the decisions made by the TSC and for the integrity of the trial.

Potential competing interests should be disclosed via the NORACT trial coordinating investigator. In many cases simple disclosure up front should be sufficient. Otherwise, the (potential) independent TSC member should remove the conflict or stop participating in the TSC. Table 1 lists potential competing interests.

x	No, I have no potential competing interests to declare
	Yes, I have potential competing interests to declare (please detail below)

Please provide details of any potential competing interests:

Name: __Niels Uldbjerg_____

Signed:  Date: _28-08-2023_____

Table 1: Potential competing interests for non-independent members

- Stock ownership in any commercial companies involved
- Stock transaction in any commercial company involved (if previously holding stock)
- Consulting arrangements with the Sponsor/Funder
- Ongoing advisory role to a company providing drugs to the trial
- Frequent speaking engagements on behalf of the intervention
- Career tied up in a product or technique assessed by trial
- Hands-on participation in the trial
- Involvement in the running of the trial
- Emotional involvement in the trial
- Intellectual conflict e.g. strong prior belief in the trial's experimental arm
- Involvement in regulatory issues relevant to the trial procedures
- Investment (financial or intellectual) or career tied up in competing products