Statistical plan

Nordic randomized trial on laparoscopic versus vaginal cerclage

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Abbreviations
eCRF – electronic case report form
PTB – preterm birth
RCT – Randomised controlled trial
ICU – intensive care unit
PROM – Prelabour rupture of membranes
PPROM – preterm prelabour rupture of membranes
c-section – caesarean section
RDS – Respiratory distress syndrome
SAE – Serious Adverse Events

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1. Trial objectives

Primary objective

- To compare laparoscopic and vaginal cerclage on preterm birth (PTB) before 32+0 weeks of gestation and on baby death in women at risk of preterm birth where the clinician has equipoise as to which treatment is better.

Secondary objectives

- To asses the effect of surgical method on maternal outcomes.
- To asses the effect of surgical method on neonatal outcomes.

Pilot study objectives

- To describe the rate of participant inclusion
- To describe the feasibility and acceptance of the interventions
- To describe the type of particpants included (see table 1 for pre-specfied patient categories)

2. Trial methods

2.1 Trial design

NORACT is an open, multicentre, randomised controlled superiority trial with an embedded internal pilot trial. The study extends from sites in Denmark, The United Kingdom, Sweden, Norway, Finland, and Iceland.

2.2 Trial interventions

Laparoscopic cerclage will be compared to transvaginal cerclage. Both procedures are widely used and accepted to prevent preterm birth. The laparoscopic cerclage is preferably inserted pre-pregnancy, but can be placed up to 10 weeks of pregnancy. This procedure is applied via key hole surgery and using general anaesthetics. The laparoscopic cerclage requires the woman to deliver by c-section. The transvaginal cerclage is inserted in gestational age 11+0-16+0 using regional anaesthetics. The transvaginal cerclage is removed later in pregnancy to allow for a vaginal birth, if otherwise advised.

2.3 Outcome measures

2.3.1 Primary outcomes:

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 end of pregnancy).

For the purpose of this document the above primary outcomes will be referred to as ‘primary outcomes’, bearing in mind that the primary outcome baby death is prioritized after the primary outcome preterm birth in a conditional hierarchical approach.

2.3.2 Secondary maternal outcomes:

- Maternal mortality – surgery related (defined as death within 30 days of the cerclage procedure).
- Maternal mortality (defined as death from time of randomisation to 42 days after end of pregnancy).
- Maternal morbidity – surgery related (defined as admission to intensive care unit (ICU) or a unit that provides 24-h medical supervision and is able to provide mechanical ventilation or continuous vasoactive drug support within 30 days of the cerclage procedure).
- Maternal morbidity (defined as admission to intensive care unit (ICU) or a unit that provides 24-h medical supervision and is able to provide mechanical ventilation or continuous vasoactive drug support from time of randomisation to 42 days after end of pregnancy).
- Harm to participant – surgery related (defined as one or more of the following: Damage to internal organs, need for re-operation, thromboembolic events, maternal cardiopulmonary arrest within 30 days of the cerclage procedure).
- Harm to participant (defined as one or more of the following: Damage to internal organs, need for re-operation, thromboembolic events, maternal cardiopulmonary arrest from time of randomisation to 42 days after end of pregnancy).
- Bleeding – surgery related (defined as blood loss > 500 ml within 30 days of the cerclage procedure).
- Bleeding – pregnancy related (defined as blood loss > 1000 ml).
- Maternal infection – surgery related (defined as infection leading to antibiotic treatment, but not ICU admission within 30 days of cerclage procedure).
- Maternal infection (defined as infection leading to antibiotic treatment, but not ICU admission from time of cerclage procedure to 42 days after end of pregnancy).
- Maternal serious infection – surgery related (defined as admission to ICU due to serious infection within 30 days of cerclage procedure).
- Maternal serious infection (defined as admission to ICU due to serious infection from time of cerclage procedure to 42 days after end of pregnancy).
- PPROM (defined as preterm prelabour rupture of membranes before 37 weeks of gestation)
- Threatened preterm labour (defined as threatened preterm labour requiring admission and intervention).
- Onset of labour (defined as spontaneous labor contractions, PROM, induction of labor or c-section).
- Mode of birth (defined as unassisted vaginal, assisted vaginal (ventouse or forceps) or caesarean section (planned, non-planned).

2.3.3 Secondary neonatal outcomes:

- Modified neonatal mortality (defined as death of a liveborn child > 22+0 weeks of gestation, time frame: 4 weeks after expected due date).

- Neonatal mortality (defined as death in the first 28 days of life > 22+0 weeks of gestation).
- Fetal loss (defined as composite of late miscarriage and stillbirth).
- Late miscarriage (defined as loss of viable pregnancy between gestational age 14+0-21+6).
- Gestational age at birth (defined as weeks and days).
- Delivery < 28 weeks.
- Delivery < 34 weeks.
- Delivery < 37 weeks.
- Birthweight (Defined as first weight in grams).
- Neonatal admission (Defined as number of consecutive days in hospital within 28 days from time of delivery. Any admission counts (SCBU, maternity ward, NICU).
- CNS morbidity (defined as Intraventricular Hemorrhage Grade III and IV and/or Periventricular leukomalacia).
- Ocular morbidity (defined as retinopathy requiring treatment).
- Gastrointestinal morbidity (defined as Necrotizing Enterocolitis (NEC) and/or SIP (Spontaneous intestinal perforation), requiring surgery).
- Respiratory support (defined as Mechanical ventilation or non-invasive ventilation).
- Respiratory distress syndrome (RDS) (defined as the need for surfactant treatment).
- Early onset neonatal infection (defined as >5 days of i.v. antibiotics, where the treatment commences within the first week of life).

2.4 Timing of outcome measures

Maternal surgical complications are measured 30 days post cerclage procedure. Remaining maternal outcomes are measured up to 42 days post delivery. Neonatal outcomes are measured up to four weeks after the expected due date.

2.5 Timing of final analysis

The final analysis for the trial will occur after the data collection for maternal and neonatal outcomes has been completed.

2.6 REDCap

Study data will be collected and managed using REDCap electronic data capture tools hosted at Aarhus University, Denmark (1). 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.

2.7 Randomisation

Eligible participants are randomly assigned to receive one of the surgical procedures in a 1:1 ratio within country strata. The randomization sequence is prepared and maintained by the Department of Clinical Medicine, Aarhus University. Participants will be randomised by a local investigator using an online 24/7 available randomisation software imbedded to REDCap. The randomisation programme will automatically transfer the entry data to the eCRF in REDCap.

2.8 Sample size

For the primary outcome 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 laparoscopic 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.(2). Since participants recruited to the NORACT trial are likely to have a somewhat lower risk of PTB compared to the aforementioned study, we assumed a baseline event rate of 20% for the vaginal cerclage group and 5% for the laparoscopic cerclage group (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 second prioritized primary outcome baby death, the proportions from Shennan et al.(2) were 21% in the vaginal cerclage group versus 3% with abdominal cerclage (2). 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 and suggest the need to prolong the recruitment period and thereby increase the sample size.

2.9 Frame work

The objective of this trial is to test the superiority of one intervention to another. The null hypothesis is that there is no difference in rate of preterm birth before 32+0 weeks of gestation between women allocated to a vaginal cerclage versus a laparoscopic cerclage. The alternative hypothesis is that there is a difference between the groups.

2.10 Interim analyses and stopping rules

No formal interim analysis is planned, however the final decision regarding an interim analysis will be made after the internal pilot trial. The data monitoring committee will evaluate pilot data after 18 months of inclusion as described in section 11 and will make recommendations to the trial steering committee with regards to how to proceed with the full trial. In the case that a interim analysis is planned at this stage, we will use the

Haybittle-Peto(3) stopping boundary of overwhelming proof of a difference of at least p<0.001. Therfore, no adjustment for multiple testing is needed.

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.

2.11 Internal pilot trial:

After a 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 (4). The NORACT board reserves the right to make smaller, necessary alterations in other methodological aspects of the pilot trial for the full trial.
The trial sites will continue recruitment during the evaluation period of the pilot study.

3 Statistical principles

3.1 Confidence intervals and p-values

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 superiorty 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. The exception is Serious Adverse Events, which may be subject to statistical testing without adjustment for multiple testing, as adjustment for multiplicity is counterproductive for considerations of safety [3].

3.2 Analysis populations

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.

We will include internal pilot data in the primary analyses. If the eligibility criteria are limited to one or more specified groups of women as a result of the pilot trial, we will perform the primary and secondary clinical analyses with only women from the embedded pilot who continue to be eligible according to the full trial criteria.

Two further analyses will be carried out for the primary (birth <32+0 weeks and baby death) outcomes only. See section 3.3. for definition of adherence and definition of the per protocol/as treated analysis and section 5.9 for details on sensitivity/supportive analyses.

3.3 Definition of adherence

Adherence to the allocated procedure will be monitored on the CRF instrument 'surgical procedure', where the procedure received is recorded. 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/additional exam-indicated vaginal cerclage in either group will count as adherent. Those women who are considered adherent will form the per-protocol (adherence) analysis. Furthermore, we will carry out an 'as treated' analysis, where participants are analysed as per what procedure they received.

3.4 Loss to follow-up

Loss to follow-up is defined as no information on date of birth or gestational age at birth.

4 Trial population

4.1 Recruitment

Patient inclusion and exclusion will be illustrated in a CONSORT flow diagram for non-pharmacologic trials(6) (see figure 1 for draft).

4.2 Baseline characteristics

Maternal, pregnancy, and surgical procedure characteristics will be tabulated as presented at the end of this report and will be presented with counts and percentages for categorical variables, mean and standard deviation for continuous normally distributed variables, and median and interquartile range for continuous non-normal variables. Ranges will be reported

where appropriate. Test of statistical significance for baseline characteristics will not be undertaken, nor confidence intervals presented.

5. Analysis methods

Intervention groups will be compared using regression models to adjust for all covariates as specified in section 5.1 where possible.

5.1 Covariate adjustment

Outcomes will, if possible ($\geq$5 events in both groups and $\geq$15 events per parameter), be analysed with adjustment for country (stratification variable), with binary regression for relative risk.

Due to an assumed low event rate in both groups, this may not be feasible and we will then proceed to and unadjusted analysis for the primary outcomes (delivery <32+0 weeks and baby death).

5.2 Distributional assumptions

Distributional assumptions (e.g. normality of regression residuals for continuous outcomes) will be assessed visually prior to analysis. First the proposed primary method of estimation in this analysis plan will be followed. If responses are considered to be particularly skewed and/or distributional assumptions violated, the impact of this will be examined through sensitivity analyses. These may consist of either transformation of responses prior to analysis (e.g. log transformation) or the use of medians and interquartile ranges alongside unadjusted differences in medians using bootstrapping methods (repetition=1000, seed=123456).

5.3 Missing data

Analysis will be completed on received data only with every effort made to follow-up participants to minimise any potential for bias. To examine the possible impact of missing data on the results, and to make sure we are complying with the intention-to-treat principle, sensitivity analyses using simple imputation will be performed on the primary outcome measures (PTB < 32+0 weeks and baby death).

5.4 Rationale for choice of statisticial model

The expected number of events for the primary outcome Delivery <32+0 including attrition and dropout are 94*0.9*0.9*0.20=15.2 in the vaginal cerclage group and 94*0.9*0.9*0.05=3.8 in the laparoscopic cerclage group. Similarly the expected number of event for the primary outcome baby death is 94*0.9*0.9*0.21=16.0 (vaginal cerclage) and 94*0.9*0.9*0.03=2.3 (laparoscopic cerclage).

The usual relative risk with approximative confidence intervals is believed to be valid when the number of events in both groups are at least 5. We therefore use the exact melded

confidence intervals of relative risk and risk difference in the reporting of the primary outcomes (7).

5.5 Analysis methods for primary outcome

The primary outcomes (delivery <32+0 weeks and baby death) will be summarised by treatment arm using frequencies and percentages. The proportion of events will be computed using the binomial model with exact confidence intervals.
The two randomisation groups will be compared using relative risk with exact confidence intervals, and Fisher's exact test will be used to compare the two proportions. We will supplement with risk differences with exact confidence intervals. The exact confidence intervals for the relative risk and risk difference will match inferences using Fisher's exact test, so the conclusion based on confidence interval and statistical test will be same.

5.6 Analysis methods for secondary outcomes

For the two continuous secondary neonatal outcome gestational age at birth and birthweight means and standard deviations will be reported alongside adjusted mean differences (with 95% confidence intervals) estimated using a linear regression model to adjust for country.

Binary maternal and neonatal outcomes will be analysed as per the primary outcome (see section 5.4). For several secondary outcomes we assume a low event rate in both groups, but where possible,we will analyse the secondary outcomes with adjustment for country (stratification variable), with binary regression for relative risk.

5.7 Analysis methods for pilot data

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 as per pre-defined risk factors as outlined 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 the predefines risk factors. No outcome data will be available for evaluation.

5.8 Safety data

The number and percentage of women and neonates experiencing any SAEs will be presented by intervention group alongside the number of events reported. Statistical significance will be determined (p-value generated) by Fisher's exact test.

5. 9 Planned subgroup analyses

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

5.10 Sensitivity analysis/supportive analysis

Sensitivity analysis will consist of:

- A per-protocol analysis (adherent, see section 3.3) for the primary outcomes only.
- An as-treated analysis (see section 3.3) for the primary outcomes only.
- A sensitivity analysis to assess distributional assumptions (where applicable, described in section 5.2) for continuous secondary outcomes.

6. Statistical software

STATA version 18.0 or higher and 'R' version 4.2.3 or higher will be used for data management and analyses.

Fig. 1: CONSORT flow diagram on inclusion and exclusion

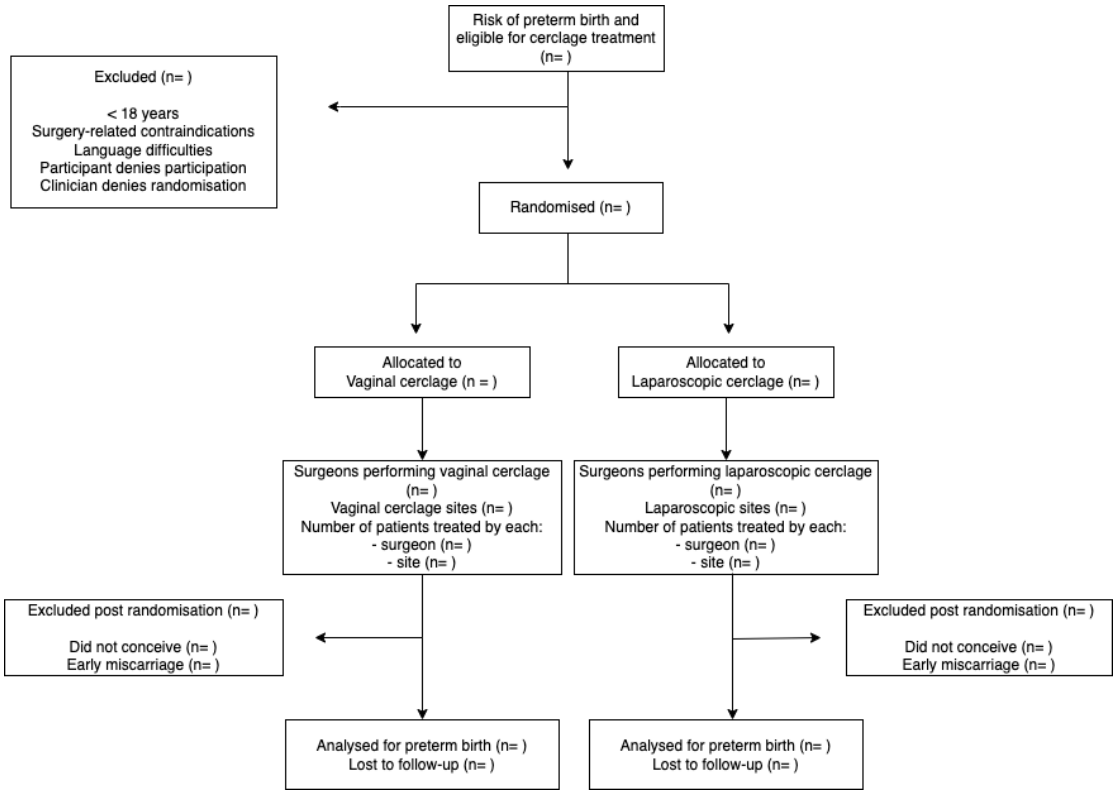
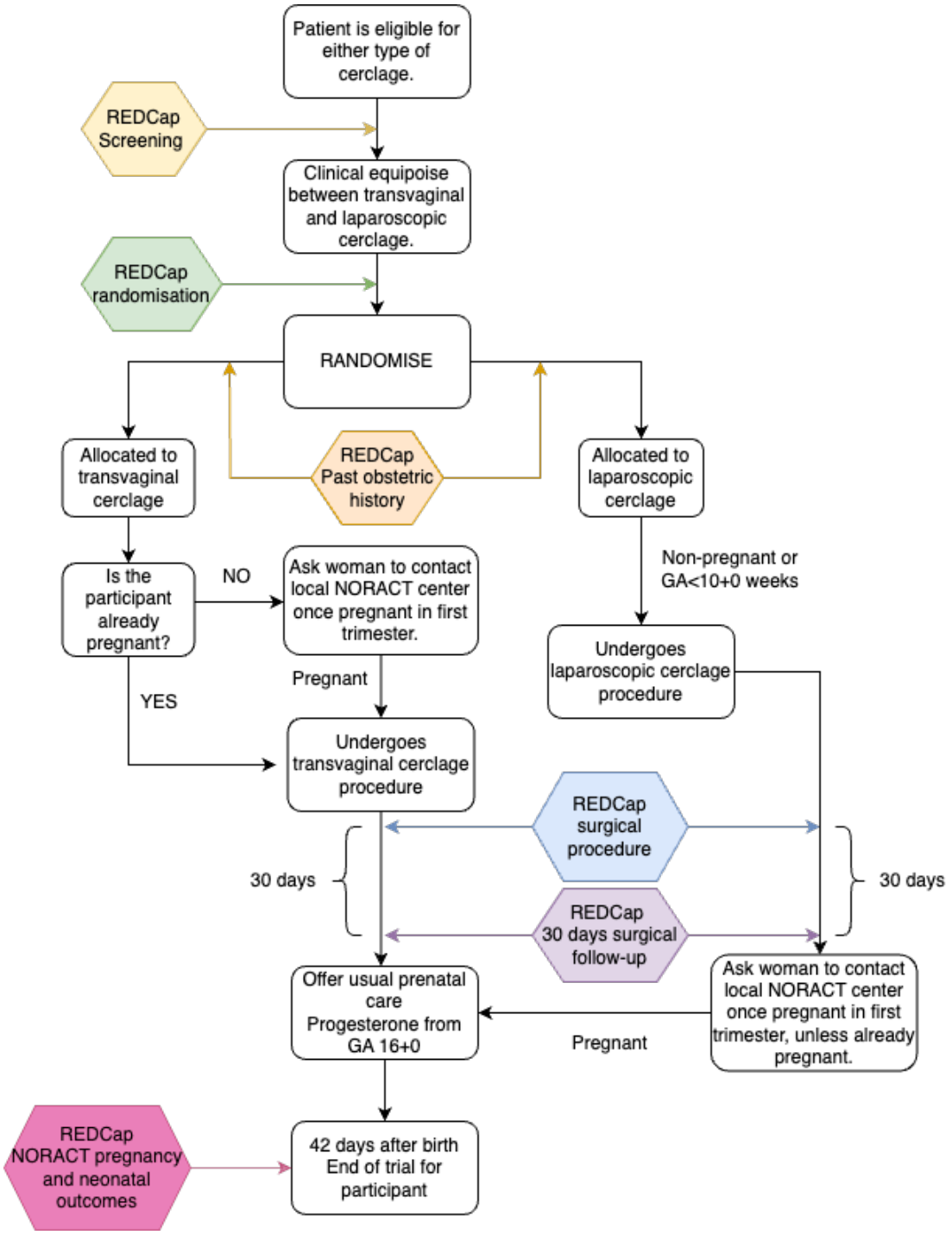


Fig. 2 Participant trial pathway



Tables

Table 1. Categories of women for sub-group 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

Table 2, Maternal characteristics	Vaginal cerclage	Laparoscopic cerclage
Maternal age, years	mean± SD	mean± SD
Parity	mean± SD	mean± SD
BMI, kg/m^2	mean± SD	mean± SD
Smoking	n (%)	n (%)
Country of residence		
- Denmark	n (%)	n (%)
- Norway	n (%)	n (%)
- Sweden	n (%)	n (%)
- Iceland	n (%)	n (%)
- Finland	n (%)	n (%)
- United Kingdom	n (%)	n (%)

Table 3, cohort risk factors for PTB	Vaginal cerclage	Laparoscopic cerclage	All
Previous Late miscarriage/PTB 14^{+0}-22^{+0} weeks 22^{+1}-28^{+0} weeks 28^{+1}- 32^{+0} weeks 32^{+1} – 37^{+0} weeks	 n (%) n (%) n (%) n (%)	 n (%) n (%) n (%) n (%)	 n (%) n (%) n (%) n (%)
Previous Planned CS Emergency CS before labour Emergency CS during 1st stage of labour Emergency CS during 2nd stage of labour	 n (%) n (%) n (%) n (%)	 n (%) n (%) n (%) n (%)	 n (%) n (%) n (%) n (%)
Previous failed elective vaginal cerclage	n (%)	n (%)	n (%)
Previous failed ultrasound indicated or exam-indicated vaginal cerclage	n (%)	n (%)	n (%)
Previous cervical surgical procedures	n (%)	n (%)	n (%)
Congenital uterine malformation - Didelphi, septum, arcuate	n (%)	n (%)	n (%)

Table 4, Primary outcomes	Vaginal cerclage	Laparoscopic cerclage	All
<32 weeks	RR + 95%CI	RR + 95%CI	RR + 95%CI
Baby death	RR + 95%CI	RR + 95%CI	RR + 95%CI

Table 5, Pregnancy outcomes (NORACT pregnancy)	Vaginal cerclage	Laparoscopic cerclage	All
Preterm birth <28 weeks <34 weeks <37 weeks	 RR + 95%CI RR + 95%CI RR + 95%CI	 RR + 95%CI RR + 95%CI RR + 95%CI	 RR + 95%CI RR + 95%CI RR + 95%CI
Gestational age at pregnancy ending, weeks and days	Median $\pm$ SD	Median $\pm$ SD	Median $\pm$ SD
Late miscarriage	n (%)	n (%)	n (%)

Table 6, NORACT pregnancy related characteristics	Vaginal cerclage	Laparoscopic cerclage	All
Treatment with vaginal progesterone	n (%)	n (%)	n (%)
Administration of tocolytics	n (%)	n (%)	n (%)
Administration of lung maturation	n (%)	n (%)	n (%)
Treatment with antibiotics Common infection Serious infection	 n (%) n (%)	 n (%) n (%)	 n (%) n (%)
Mode of conception - Spontaneous - ART	 n (%) n (%)	 n (%) n (%)	 n (%) n (%)
Multiple gestation	n (%)	n (%)	n (%)
Threatened preterm labour	n (%)	n (%)	n (%)
PPROM	n (%)	n (%)	n (%)
Onset of labour Spontaneous labour contractions Induction of labour C-section	 n (%) n (%) n (%)	 n (%) n (%) n (%)	 n (%) n (%) n (%)
Mode of birth Unassisted vaginal Assisted vaginal (forceps or ventouse) Planned CS Non-planned CS	 n (%) n (%) n (%) n (%)	 n (%) n (%) n (%) n (%)	 n (%) n (%) n (%) n (%)
Rescue cerclage	n (%)	n (%)	n (%)

Table 7, Characteristics of cerclage procedure	Vaginal cerclage	Laparoscopic cerclage
Number of procedures	n (%)	n (%)
Number of sites	n (%)	n (%)
Number of surgeons	n (%)	n (%)
Surgeon's experience, years	Mean ± SD	Mean ± SD
Type of cerclage - Purse string with bladder mobilisation - Purse string without bladder mobilisation	 n (%) n (%)	N/A
Timing of procedure Pre-pregnancy During pregnancy	 n (%)	 n (%) n (%)
Gestational age at placement, week and days	Mean ± SD	Mean ± SD
Anaesthesia - General - Regional	 n (%) n (%)	 n (%) n (%)

- Conversion from regional to general during procedure	n (%)	n (%)
Number of sutures 1 2	 n (%) n (%)	 n (%) n (%)
Type of suture Multifilament Monofilament	 n (%) n (%)	 n (%) n (%)
Antibiotics	n (%)	n (%)
Admission to hospital, days	Median ± SD	Median ± SD
Cervical length Overall closed length of cervix Length from stitch to external os Funneling present	 Mean ± SD Mean ± SD n (%)	 Mean ± SD Mean ± SD n (%)
Duration of surgery, minutes	Median ± SD	Median ± SD
Blood loss, ml	Mean ± SD	Mean ± SD
Complications (within 30 days from the procedure)	n (%)	n (%)
Manipulator applied to the uterus	N/A	n (%)
Additional procedures performed during procedure	N/A	n (%)

Table 8, Neonatal outcomes	Vaginal cerclage	Laparoscopic cerclage	All
Baby death sub groups: Any loss Still birth Death of a liveborn infant	 n (%) n (%) n (%)	 n (%) n (%) n (%)	 n (%) n (%) n (%)
Fetal loss	n (%)	n (%)	n (%)
Neonatal mortality	n (%)	n (%)	n (%)
Birth weight (g)	Mean ± SD	Mean ± SD	Mean ± SD
Neonatal admission, days	Median ± SD	Median ± SD	Median ± SD
CNS morbidity	n (%)	n (%)	n (%)
Retinopathy of prematurity	n (%)	n (%)	n (%)
Gastrointestinal morbidity	n (%)	n (%)	n (%)
Respiratory support	n (%)	n (%)	n (%)
Respiratory Distress Syndrome (RDS)	n (%)	n (%)	n (%)
Early onset infection	n (%)	n (%)	n (%)

References

1. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. Journal of Biomedical Informatics. 2009;42(2):377-81.
2. Shennan A, Chandiramani M, Bennett P, David AL, Girling J, Ridout A, et al. MAVRIC: a multicenter randomized controlled trial of transabdominal vs transvaginal cervical cerclage. Am J Obstet Gynecol. 2020;222(3):261 e1- e9.
3. Peto R, Pike MC, Armitage P, Breslow NE, Cox DR, Howard SV, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. I. Introduction and design. Br J Cancer. 1976;34(6):585-612.
4. Charlesworth G, Burnell K, Hoe J, Orrell M, Russell I. Acceptance checklist for clinical effectiveness pilot trials: a systematic approach. BMC Medical Research Methodology. 2013;13(1):78.
5. Dmitrienko A, D'Agostino RB, Sr., Huque MF. Key multiplicity issues in clinical drug development. Stat Med. 2013;32(7):1079-111.
6. Boutron I, Altman DG, Moher D, Schulz KF, Ravaud P, Group CN. CONSORT Statement for Randomized Trials of Nonpharmacologic Treatments: A 2017 Update and a CONSORT Extension for Nonpharmacologic Trial Abstracts. Ann Intern Med. 2017;167(1):40-7.
7. Fay MP, Proschan MA, Brittain E. Combining one-sample confidence procedures for inference in the two-sample case. Biometrics. 2015;71(1):146-56.