Statistical Analysis Plan

FINAL

Version 1.0

Measurement of cervical length with vaginal ultrasound in the second trimester in asymptomatic women with a singleton pregnancy to predict preterm delivery: a Swedish multi-center observational study

2018-03-13

Approvals

Name/Title: Mattias Molin / Statistician Signature:	Date
Name/Title: Lil Valentin/ Co-worker, Professor Signature:	Date
Name/Title: Ulla-Britt Wennerholm / Co-worker, Associate professor Signature:	Date 14/3-18

Table of Contents

LIST OF ABBREVIATIONS

Abbreviation	Definition
CRF	Case Record Form
eCRF	Electronic Case Record Form
FAS18W	Full Analysis Set 18W: includes all women with cervical measurement at gestational week 18+0-20+6
FAS18W21W	Full Analysis Set 18W21W: includes all women with cervical measurement both at gestational week 18+0-20+6 and 21+0-23+6
FAS21W	Full Analysis Set 21W: includes all women with cervical measurement at gestational week 21+0-23+6
GW	Gestational week
MBR	Medical Birth Register
NPR	National Patient Register
NOFAS	Includes enrolled women without cervical measurement but who agreed to us collecting data
PTD	Preterm Delivery
ROC-curve	Receiver Operating Characteristic curve
sPTD	Spontaneous preterm delivery
SWE1417	A background population from the Pregnancy Register consisting of all singleton deliveries (one delivery per woman [first delivery during the study period if there is more than one] during the study period) between 2014 and 2017 (details below), maternal age ≥18 years
SWE1417nomalf	SWE1417 but excluding deliveries with a child with any malformation (International Classification of Diseases [ICD]10 Q-codes)
FAS18Wnomalf	FAS18W but excluding deliveries with a child with any malformation (ICD10 Q-codes]). To be used only for comparison with SWE1417nomalf regarding demographical, pregnancy, delivery and neonatal variables.

1 STUDY DETAILS

1.1 Study Objectives

The general aim is to collect information about screening for preterm delivery (PTD) with cervical length measurements at mid-gestation in asymptomatic women with a singleton pregnancy in Sweden, and to use the results to plan a randomized controlled trial to investigate the effect on PTD of such screening followed by prophylactic treatment.

The specific aims are to - in a Swedish population:

1) find the optimal cervical length cut-off to predict PTD in asymptomatic women with a singleton pregnancy
2) estimate the sensitivity and specificity with regard to PTD of "short" cervix as measured by vaginal ultrasound (using different measurement techniques and definitions) at mid-gestation in asymptomatic women with a singleton pregnancy
3) define the optimal gestational length (18+0 to 20+6 or 21+0 to 23+6 gestational weeks [GW]) to measure cervical length to predict PTD in asymptomatic women with a singleton pregnancy
4) investigate if a shortening of the cervix between 18+0-20+6 GW and 21+0-23+6 GW is more predictive of PTD than a single measurement of cervical length in asymptomatic women with a singleton pregnancy
5) estimate the prevalence of "short" cervix (as defined on the basis of the results of this study) as measured by vaginal ultrasound at mid-gestation in asymptomatic women with a singleton pregnancy
6) based on the results of 1), 2), 3) 4) and 5) and knowledge of the prevalence of PTD in singleton pregnancies in Sweden calculate the sample size of a Swedish randomized controlled trial to investigate the effect on PTD and neonatal outcome of screening asymptomatic women with a singleton pregnancy with ultrasound measurement of cervical length followed by prophylactic treatment if the cervix is "short"

1.2 Study Design

Swedish prospective observational multicentre study. Case record form (CRF) data will be merged with data from The Swedish Pregnancy Register, the Medical Birth Register, the National Patient Register and the Swedish Prescribed Drug Register (Läkemedelsregistret) (only data on prescribed [=expedited] progesterone during pregnancy).

1.3 Treatment Groups

This is an observational study without any treatment groups.

1.4 Sample Size

11000 women; 100 of these women (0.9% of 11000) are expected to have their delivery before 33+0 GW, which gives a reasonable 95%CI for estimated sensitivity of "short cervix" to predict PTD before 33+0 GW.

2 STUDY POPULATIONS

Eligibility criteria: asymptomatic women ≥ 18 years old with a live singleton pregnancy, who are able to understand oral or written information (information leaflets are available in Arabic, Bosnian, Croatian, Serbian, English, Farsi, Spanish and Somali language).

Inclusion criteria: eligible women who give oral and written informed consent to participate.

Exclusion criteria: women with fetal malformation, preterm prelabor rupture of membranes, current vaginal bleeding, ongoing miscarriage, cerclage in situ, progesterone treatment, all at the time of recruitment, are not eligible for inclusion. Women with missing information on pregnancy outcome will be excluded.

2.1 Definition of Study Populations

Subjects fulfilling the eligibility criteria but not the exclusion criteria will be included in the Full Analyses Sets (FASs). To be included in the Full Analysis Set 18W (FAS18W) there must be results of cervical length measurements performed at 18+0 to 20+6 GW. Pregnancy terminations are excluded (variable "Graviditetsreg. avslutas orsak" with value "Vet ej" will be manually scrutinized to elucidate the reason for no further information in the Pregnancy register).

A second analysis set includes subjects with a cervical length measurement at 21+0 to 23+6 GW (FAS21W). Subjects with a cervical measurement only at 21+0 to 23+6 GW (no measurement at 18+0 to 20+6 GW) will be included in FAS21W as well as those with a cervical length measurement both at 18+0 to 20+6 GW and 21+0 to 23+6 GW. To be included in the FAS21W there must be results of cervical length measurements performed at 21+0 to 23+6 GW. Pregnancy terminations are excluded (variable "Graviditetsreg. avslutas orsak" with value "Vet ej" will be manually scrutinized to elucidate the reason for no further information in the Pregnancy register).

A third analysis set includes subjects included in both FAS18W and FAS21W (FAS18W21W). To be included in FAS18W21W subjects must have a cervical measurement both at 18+0 to 20+6 GW and 21+0 to 23+6 GW and at least 14 days must have elapsed between the two measurement occasions for subjects to be included in this analysis set.

Subjects not included in any of the FASs but who agreed to us collecting data from The Pregnancy Register and the Swedish Prescribed Drug Register (NOFAS) will be analysed demographically, with regard to some pregnancy, delivery and neonatal variables and with regard to PTD frequency. Pregnancy terminations are excluded (variable "Graviditetsreg. avslutas orsak" with value "Vet ej" will be manually scrutinized to elucidate the reason for no further information in the Pregnancy register).

A woman can participate ONLY once in the study. One subject is allowed to participate only once with cervical measurements in a FAS population. The pregnancy with most information will be included: if one pregnancy has measurements both at 18-20 weeks and at 21-23 weeks, then that pregnancy will have priority for inclusion over a pregnancy with only one of the two measurements. If there is only one measurement occasion per pregnancy, then the first pregnancy with a measurement during the study period will be included in the FAS. If a woman has

been included more than once in FAS the first pregnancy with most complete outcome data will be included (important).

If a woman has been included with one pregnancy in NOFAS and with another pregnancy in a FAS, then the pregnancy in NOFAS will be excluded, provided that the pregnancy in FAS has outcome data.

One subject is allowed to participate only once in NOFAS. If a woman has been included more than once in NOFAS the first pregnancy with outcome data will be included.

A background population from the Pregnancy Register consisting of all deliveries (singletons, one delivery per subject, first delivery during the study period if there is more than one) (SWE1417) will be analysed demographically and by PTD frequency and with regard to some other pregnancy, delivery and neonatal outcomes. The study populations (FASs and NOFAS) will not be excluded from SWE1417. The same background population but excluding deliveries with a child with any malformation (all Q-codes in ICD10) (SWE1417nomalf) will be analysed demographically, and with regard to some pregnancy, delivery and neonatal variables, and by PTD frequency to be compared with FAS18Wnomalf (i.e. FAS18W excluding deliveries with a child with any malformation [all Q-codes in ICD10]). The time period will be defined from date of the first delivery occurring during the study period to the last delivery occurring during the study period in the FAS18W population.

3 STUDY VARIABLES

3.1 Baseline maternal variables

Baseline Characteristics

- Age (preg reg)*
- Ethnicity (eCRF, only for FAS and NOFAS)*
- Country of origin (preg reg) grouped as SCB model
- Highest level of education (preg reg)*
- Main occupation (working, student) (preg reg)
- Height at first antenatal visit (preg reg)*
- Weight at first antenatal visit (preg reg)
- BMI at first antenatal visit (preg reg)*
- Smoking status 3 months before pregnancy (preg reg)
- Smoking status at start of pregnancy (preg reg)*
- Smoking status at 30-32 GW (pregn reg)
- Snuff status 3 months before pregnancy (preg reg)
- Snuff status at start of pregnancy (preg reg)*
- Snuff status at 30-32 GW (preg reg)
- Involuntary childlessness (preg reg)*
- Years of involuntary childlessness (preg reg)*
- IVF in current pregnancy (preg reg)*
- Chronic hypertension (preg reg)*
- Diabetes type 1 or 2 (preg reg)*
- Renal disease (preg reg)*
- Prior surgery of cervix (for main study: National Patient Register [NPR, outpatient visits, in-patient care]; for subgroup analysis of high risk groups in FAS and NOFAS: NPR, eCRF and scrutiny of individual medical records)*
- Number of previous pregnancies (preg reg)*

- Number of previous late miscarriages (GW 14+0-21+6) (not for main study but for subgroup analysis of high risk groups in FAS and NOFAS: eCRF, scrutiny of individual medical records)
- Number of previous PTDs (<37 GW) (MBR; for subgroup analysis of high risk groups in FAS and NOFAS: MBR, eCRF, scrutiny of individual medical records)*
- Number of previous spontaneous PTDs (<37 GW) (MBR; for subgroup analysis of high risk groups in FAS and NOFAS: MBR; eCRF, scrutiny of individual medical records)*
- Number of previous iatrogenic PTDs (<37 GW) (MBR; for subgroup analysis of high risk groups in FAS and NOFAS: MBR; eCRF, scrutiny of individual medical records)*
- Number of previous stillbirths (preg reg)*
- Number of previous live births (preg reg)*
- Parity (preg reg)*
- Audit (risk evaluation) at first antenatal visit (preg reg)*
- Number of pregnancy controls by midwife (preg reg)
- Number of pregnancy controls by doctor (preg reg)

*) Included in univariable models and possible variable in the multivariable models when predicting PTD, sPTD and iPTD (see section 4.4.3 Exploratory Analyses).

3.2 Efficacy Variables

3.2.1 General

All cervical lengths will be rounded to nearest integer (mm) if decimal integer has been entered into the database. This will be made prior to any other calculations.

Predicting variables for primary and secondary efficacy variables

Predicting variables for FAS18W and FAS 21W:

Cervical lengths at 18+0 to 20+6 and at 21+0 to 23+6 GW (for minimal, maximal and mean of the three measurements):

- A-B (length of the closed cervical canal)
- A-C (if no isthmus A-C= A-B)
- Isthmus YES or isthmus NO
- A-B+B-C (closed cervical canal+isthmus) (if no isthmus this is A-C = A-B)
- B-C (length of the isthmus zero included)
- B-C (length of the isthmus zero not included)

Additional variables for FAS1821W

- Change of A-B and A-C between 18+0 to 20+6 and 21+0 to 23+6 GW (expressed as (percentage of cervix 1)
- Change in mm of A-B and A-C between 18+0 to 20+6 and 21+0 to 23+6 GW
- Change (mm) of B-C between 18+0 to 20+6 and 21+0 to 23+6 GW
- Change Isthmus YES to isthmus NO compared to all others

The cervical length measurements are illustrated in Figure 1. Each measurement is taken three times, and all three are recorded.

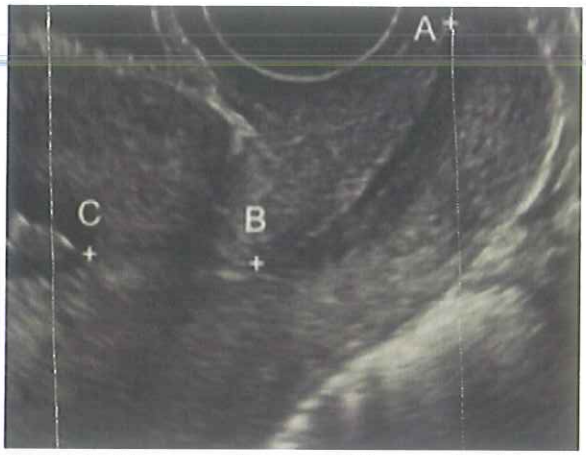

Figure 1. Ultrasound image of the cervix obtained with vaginal ultrasound. A, outer cervical os; B, inner cervical os; C, the virtual inner cervical os created by the opposition of the anterior and posterior isthmus. The following measurements are taken: A-B (length of the closed cervical canal); B-C (length of the isthmus); A-C. A fourth measurement result is obtained by adding (A-B) and (B-C).

3.2.2 Primary Efficacy Variable

Endpoint variable: Preterm delivery (delivery between 22+0 to 32+6 GW). Stillbirths are included in preterm delivery. Late miscarriages (before 22+0 GW) are excluded in the analyses.

3.2.3 Secondary Efficacy Variables

Endpoint variables: Preterm delivery defined as either of:

- <33+0 GW (Same as primary but also includes late miscarriage defined as miscarriage after inclusion and before 22+0 GW)
- <28+0 GW, includes late miscarriage <22+0 GW
- <29+0 GW, includes late miscarriage <22+0 GW
- <30+0 GW, includes late miscarriage <22+0 GW
- <31+0 GW, includes late miscarriage <22+0 GW
- <32+0 GW, includes late miscarriage <22+0 GW
- <34+0 GW, includes late miscarriage <22+0 GW
- <35+0 GW, includes late miscarriage <22+0 GW
- <36+0 GW, includes late miscarriage <22+0 GW
- <37+0 GW, includes late miscarriage <22+0 GW

+Same definitions but separate analysis for spontaneous PTD (sPTD) and iatrogenic PTD (defined by variables [as spontaneous onset of labour, induction of labour, prelabour caesarean delivery] and ICD diagnoses in Pregnancy Register and scrutiny of medical records if unclear)

The prevalence of "short cervix" (using different definitions) will be calculated. Short cervix will be defined within the frame of the project, but the prevalence of the following lengths (minimal A-B and minimal A-C) will also be calculated: 10-20mm, ≤15mm, ≤25mm.

3.2.4 Exploratory Variables

- Vaginal progesterone treatment (from the Swedish Prescribed Drug Register) during pregnancy defined as expedited progesterone any time between 18 and 37 GW
- Cervical cerclage treatment (data collected from the Pregnancy Register, the Patient Register and scrutiny of medical records. KVÅ code: MAB00, MAB03)

3.3 Pregnancy, delivery and neonatal variables

- Pre-eclampsia or gestational hypertension ICD 10: O13.9, O14 with decimals, O15 with decimals (preg reg)
- Chronic hypertension ICD 10: O10 with decimals (preg reg)
- Diabetes type 1, 2 or gestational diabetes ICD 10: O24 with decimals (preg reg)
- Mode of delivery (preg reg)
    - Spontaneous vaginal
    - Assisted vaginal (forceps or vacuum extraction)
    - Caesarean delivery
        - Planned
        - Emergency
- Gestational age at delivery (days) (preg reg)
- PTD (<33 GW) sPTD or iatrogenic PTD (preg reg)
- PTD (<37 GW) sPTD or iatrogenic PTD (preg reg)
- Birth weight (g) (preg reg)
- SGA, defined according to Marsal et al, 1996 (preg reg)
- Stillbirth after 22+0 GW (before or during labor) (preg reg)
- Death within 7 days after birth (preg reg)
- Late miscarriage (before 22+0 GW) (preg reg (variable "Graviditetsreg. avslutas orsak" with value "Missfall före vecka 22+0", cases with "avslutas orsak ej angiven and all other cases, too will also be manually scrutinized))
- Malformations (ICD 10 Q-codes) (preg reg)
- Apgar score at 1, 5, 10 minutes (preg reg)
- Onset of delivery (preg reg)
    - Induction of labour
    - Spontaneous onset
    - Planned caesarean delivery

4 STATISTICAL METHODOLOGY

4.1 General Methodology

Continuous data will be presented with mean, standard deviation, median, min, max and number of subjects. Categorical data will be presented with number of subjects and percent.

When studying PTD, the frequency (prevalence of PTD) will be presented overall and by intervals of the cervical length. Odds ratio (with 95% CI and p-value) based on continuous cervical length in mm will be presented along with the receiver operating characteristic (ROC) curve and Area under the ROC-curve (with 95% CI) using logistic regression. Sensitivity, specificity, positive and negative likelihood ratio with their 95% CI will be calculated for the cervical length corresponding to the point on the ROC curve closest to the upper left corner and for the cervical length cut-off judged to

be clinically optimal (based on how one judges the relative importance of sensitivity and specificity, see below).

The optimal method for measuring the cervix (which measurement, i.e. minimal, maximal or mean A-B, A-C, B-C or A-B plus B-C, or change between two measurement occasions in any of the measurements; which GW, i.e. 18 to 20 weeks or 21 to 23 weeks) and the optimal cervical length cut-off of the optimal method to predict PTD <33+0 GW will be identified. The final cut-off will be chosen on the basis of clinical judgement (relative importance of sensitivity and specificity), but the mathematically best cut off will also be reported.

The prevalence of short cervix (short cervix defined as length below or equal to the cut-off we have selected on the basis of our results) will be estimated. In addition the prevalence of cervical length (minimal A-B and minimal A-C) 10-20mm, <=15mm and <=25mm will be estimated. The descriptives Mean, SD, median, Q1, Q3, min and max for all the cervical lengths measurements will also be presented.

Analyses will be made totally as well as separately for sPTD and iatrogenic PTD. When analysing sPTD <33+0 GW, iatrogenic PTD <33 weeks will be kept in the denominator when calculating specificity (i.e., all non-sPTD <33 GW in denominator when calculating specificity). When analysing iatrogenic PTD, sPTD will be kept in the denominator when calculating specificity (i.e., all non-iatrogenic PTD <33 GW in denominator when calculating specificity).

Women with missing information on pregnancy outcome will be excluded in the analysis.

All tests will be two-tailed and conducted at 0.05 significance level. All analyses will be performed by using SAS® v9.4 (Cary, NC).

4.2 Disposition of subjects

Number of subjects in each population totally and by centre will be presented.

4.3 Baseline characteristics

Baseline characteristics will be summarized for the FAS18W, FAS21W, FAS18W21W, NOFAS, SWE1417, SWE1417nomalf and FAS18Wnomalf populations and analyzed according to the methods described in section "General Methodology" above.

Comparisons of PTDs will be made by FAS18W with NOFAS and SWE1417. FAS18Wnomalf will be compared with SWE1417nomalf. No formal statistical testing will be performed.

4.4 Efficacy Analyses

4.4.1 Primary Efficacy Analysis

When studying primary endpoint (PTD [delivery between 22+0 to 32+6 GW]), for FAS18W the frequency (prevalence of PTD) will be presented overall and by intervals of the cervical length. Odds ratio (with 95% CI and p-value) based on continuous cervical length in mm will be presented along with the ROC curve and Area under the ROC-curve (with 95% CI) using logistic regression. Sensitivity, specificity, positive and negative likelihood ratio with their 95% CI will be calculated for the cervical length corresponding to the point on the ROC curve closest to the upper left corner

(mathematically best cut-off) and for the cervical length cut-off judged to be clinically optimal (relative importance of sensitivity and specificity, see below).

In addition, a logistic model with piecewise linear cervix length will be evaluated. Same statistics as for the model above.

4.4.2 Secondary Efficacy Analyses

See method described in 4.1.

Scatter plots for cervical lengths (y) vs GW at delivery (x) will be produced for all different measures of the cervical length. Boxplots (with mean added) of cervical lengths vs GW at delivery (categorized as integer week) will also be produced.

In order to find independent predictors of PTD of <33 GW and <37 GW a stepwise logistic regression will be performed including cervical length variables at 18+0 to 20+6 and at 21+0 to 23+6 GW (including the change variables). This will help determine which cervical length measure best predicts PTD.

4.4.3 Exploratory Analyses

Selected analyses of those described above will be performed with and without subjects who were expedited vaginal progesterone and with and without subjects who received cervical cerclage after the cervical length measurement. This will serve as a sensitivity analysis. In addition, cervical length in the subjects who have been expedited progesterone or treated with cerclage during the pregnancy will be compared to the cervical lengths of all other subjects.

Univariable and multivariable prediction modelling of PTD, sPTD and iPTD will be performed using selected baseline variables (see section 3.1.1 including marked (*) variables) and cervical lengths variables as independent possible predictors. Stepwise selection will be used to determine which variables best predict PTD. ROC curves for the combination and for each independent variable in the final model will be presented.

4.4.4 Pregnancy, delivery and neonatal analysis

Pregnancy, delivery and neonatal variables will be summarized for the FAS18W, FAS21W, FAS18W21W, NOFAS, SWE1417, SWE1417nomalf and FAS18Wnomalf populations and analyzed according to the methods described in section "General Methodology" above.

Comparisons of PTDs will be made by FAS18W with NOFAS and SWE1417. FAS18Wnomalf will be compared with SWE1417nomalf. No formal statistical testing will be performed.

4.4.5 Subgroup analysis

Same analyses as outlined above (primary analysis section 4.4.1) will be performed in a selected high risk group of women with a previous sPTD or late miscarriage in a singleton pregnancy (late miscarriage 14+0-21+6 GW). Women with a previous late miscarriage will be identified from eCRF and by scrutiny of medical records. Previous sPTD will be identified from eCRF and by scrutiny of medical records and MBR.

Same analyses as above (primary analysis section 4.4.1) will also be performed in a group of women with a previous cervical conization. Women with a previous cervical surgery will be identified from eCRF and by scrutiny of medical records and from PR (inpatient and outpatient care).

5 LISTING OF TABLE, FIGURES AND LISTINGS

5.1 Listing of Tables

General: Some tables will be produced for different definitions of preterm delivery, different cervical lengths and different populations which will generate multiple tables [x].

Table Number	Table Title
1	Disposition of patients
2.1	Demographics and baseline characteristics by population
2.2	Descriptive tabulation of Pregnancy, delivery and neonatal variables
3.1	Presentation of cervical measurements (prevalence and descriptives) by population
3.2.x	Analysis of PTD by cervical length (see mock table below)
4.1	Results from multivariable stepwise logistic regressions of preterm delivery (cervical lengths)
4.2	Results from univariable and multivariable stepwise logistic regressions of preterm delivery (baseline variables and cervical lengths)
5	Prevalence of "short cervix" (using different definitions)

Selected tables/analyses/figures will be performed for the subgroups defined and for subjects with no known use of progesterone or cerclage.

Mock table of Table 3.x

[Tables like this will be produced. PTD cutoff, timepoint, measurement (A-B, A-C etc) and cervical measurement (minimal, maximal or mean) may be part of the table or as table selection. In the example below timepoint and measurement (A-B, A-C etc) is part of the table and PTD cutoff, cervical measurement (minimal, maximal or mean) serves as table selection.]

Table 3.x Analysis of PTD (<33+0 GW) by minimal (of three measurements) cervical lengths (FAS18W subjects)

Time-point	Measurement	Total #PTD (n %)	#PTD <Q1 (n %)	#PTD Q1-Q2 (n %)	#PTD Q2-Q3 (n %)	#PTD >Q3 (n %)	CR (95% CI)	p	AUC (95% CI)	Cut-off Ma/Cl	Sens Ma/Cl	Spec Ma/Cl	LR- Ma/Cl	LR+ Ma/Cl
18+0 to 20+6	A-B	xx (x.x%)	xx (x.x%)	xx (x.x%)	xx (x.x%)	xx (x.x%)	x.xx (x.xx; x.xx)	x.xxxx	xxx (x.xx; x.xx)	xx.x xx.x	xx.x xx.x	xx.x xx.x	x.xx x.xx	x.xx x.xx
	A-C	xx (x.x%)	xx (x.x%)	xx (x.x%)	xx (x.x%)	xx (x.x%)	x.xx (x.xx; x.xx)	x.xxxx	xxx (x.xx; x.xx)	xx.x xx.x	xx.x xx.x	xx.x xx.x	x.xx x.xx	x.xx x.xx
	stimulus	xx (x.x%)	xx (x.x%)	xx (x.x%)	xx (x.x%)	xx (x.x%)	x.xx (x.xx; x.xx)	x.xxxx	xxx (x.xx; x.xx)	xx.x xx.x	xx.x xx.x	xx.x xx.x	x.xx x.xx	x.xx x.xx
	A-B+B-C	xx (x.x%)	xx (x.x%)	xx (x.x%)	xx (x.x%)	xx (x.x%)	x.xx (x.xx; x.xx)	x.xxxx	xxx (x.xx; x.xx)	xx.x xx.x	xx.x xx.x	xx.x xx.x	x.xx x.xx	x.xx x.xx
	B-C (w/th C)	xx (x.x%)	xx (x.x%)	xx (x.x%)	xx (x.x%)	xx (x.x%)	x.xx (x.xx; x.xx)	x.xxxx	xxx (x.xx; x.xx)	xx.x xx.x	xx.x xx.x	xx.x xx.x	x.xx x.xx	x.xx x.xx
	B-C (w/thout C)	xx (x.x%)	xx (x.x%)	xx (x.x%)	xx (x.x%)	xx (x.x%)	x.xx (x.xx; x.xx)	x.xxxx	xxx (x.xx; x.xx)	xx.x xx.x	xx.x xx.x	xx.x xx.x	x.xx x.xx	x.xx x.xx
21+0 to 23+6	A-B	xx (x.x%)	xx (x.x%)	xx (x.x%)	xx (x.x%)	xx (x.x%)	x.xx (x.xx; x.xx)	x.xxxx	xxx (x.xx; x.xx)	xx.x xx.x	xx.x xx.x	xx.x xx.x	x.xx x.xx	x.xx x.xx
	A-C	xx (x.x%)	xx (x.x%)	xx (x.x%)	xx (x.x%)	xx (x.x%)	x.xx (x.xx; x.xx)	x.xxxx	xxx (x.xx; x.xx)	xx.x xx.x	xx.x xx.x	xx.x xx.x	x.xx x.xx	x.xx x.xx
	stimulus	xx (x.x%)	xx (x.x%)	xx (x.x%)	xx (x.x%)	xx (x.x%)	x.xx (x.xx; x.xx)	x.xxxx	xxx (x.xx; x.xx)	xx.x xx.x	xx.x xx.x	xx.x xx.x	x.xx x.xx	x.xx x.xx
	A-B+B-C	xx (x.x%)	xx (x.x%)	xx (x.x%)	xx (x.x%)	xx (x.x%)	x.xx (x.xx; x.xx)	x.xxxx	xxx (x.xx; x.xx)	xx.x xx.x	xx.x xx.x	xx.x xx.x	x.xx x.xx	x.xx x.xx
	B-C (w/th C)	xx (x.x%)	xx (x.x%)	xx (x.x%)	xx (x.x%)	xx (x.x%)	x.xx (x.xx; x.xx)	x.xxxx	xxx (x.xx; x.xx)	xx.x xx.x	xx.x xx.x	xx.x xx.x	x.xx x.xx	x.xx x.xx
	B-C (w/thout C)	xx (x.x%)	xx (x.x%)	xx (x.x%)	xx (x.x%)	xx (x.x%)	x.xx (x.xx; x.xx)	x.xxxx	xxx (x.xx; x.xx)	xx.x xx.x	xx.x xx.x	xx.x xx.x	x.xx x.xx	x.xx x.xx
Change 18+0 to 20+6 to 21+0 to 23+6	A-B (% of cervix l)	xx (x.x%)	xx (x.x%)	xx (x.x%)	xx (x.x%)	xx (x.x%)	x.xx (x.xx; x.xx)	x.xxxx	xxx (x.xx; x.xx)	xx.x xx.x	xx.x xx.x	xx.x xx.x	x.xx x.xx	x.xx x.xx
	A-B (m/m)	xx (x.x%)	xx (x.x%)	xx (x.x%)	xx (x.x%)	xx (x.x%)	x.xx (x.xx; x.xx)	x.xxxx	xxx (x.xx; x.xx)	xx.x xx.x	xx.x xx.x	xx.x xx.x	x.xx x.xx	x.xx x.xx
	A-C (% of cervix l)	xx (x.x%)	xx (x.x%)	xx (x.x%)	xx (x.x%)	xx (x.x%)	x.xx (x.xx; x.xx)	x.xxxx	xxx (x.xx; x.xx)	xx.x xx.x	xx.x xx.x	xx.x xx.x	x.xx x.xx	x.xx x.xx
	A-C (m/m)	xx (x.x%)	xx (x.x%)	xx (x.x%)	xx (x.x%)	xx (x.x%)	x.xx (x.xx; x.xx)	x.xxxx	xxx (x.xx; x.xx)	xx.x xx.x	xx.x xx.x	xx.x xx.x	x.xx x.xx	x.xx x.xx
	B-C (m/m)	xx (x.x%)	xx (x.x%)	xx (x.x%)	xx (x.x%)	xx (x.x%)	x.xx (x.xx; x.xx)	x.xxxx	xxx (x.xx; x.xx)	xx.x xx.x	xx.x xx.x	xx.x xx.x	x.xx x.xx	x.xx x.xx
	stimus YES to NO compared to all other	xx (x.x%)					x.xx (x.xx; x.xx)	x.xxxx	xxx (x.xx; x.xx)	xx.x xx.x	xx.x xx.x	xx.x xx.x	x.xx x.xx	x.xx x.xx

Ma, mathematically best cutoff; Cl, clinically selected cutoff: CI, confidence interval

5.2 Listing of Figures

General: The figures will be produced for different definitions of preterm deliveries, different cervical measurements and different populations which will generate multiple figures [x].

Figure Number	Figure Title
1.1.x	Scatter plot for cervical lengths vs GW at delivery
1.2.x	Box plots for cervical lengths vs GW at delivery (categorised per week; mean added)
2.x	PTD ROC curve by cervical length and multivariable models