Supplement 2: Statistical Analysis plan

The variables and statistical analysis plan are available in the CIP and at clinicaltrials.gov.

Plan as described in CIP

The primary outcome will be evaluated as percent of events. The difference in events between the two arms will tested according to Wald, using a p-value of 0.05.

Time to primary outcome will be described according to Kaplan-Meier and the difference between the two arms will be compared using the logrank test.

Descriptive measures of primary and secondary outcomes will be tabulated for each arm and differences between the arms will be assessed using Student's t-test or Fisher's exact test, where appropriate.

Relations between the primary event and confounding variables will be investigated using a logistic regression model and tested according to Wald.

All analysis will be made according to intention to treat using a p-value of 0.05, adjusted according to Bonferroni for multiple comparisons.

Plan as described in clinicaltrials.gov

The primary outcome is delivery room intubation or death. The secondary outcomes include time to intubation, use of surfactant, use of positive pressure ventilation, respiratory support at 72 hours and temperature on intensive care admission. Safety variables include pneumothorax, intraventricular haemorrhage and problems with ventilation and equipment.

All analysis will be on intention to treat and $p<0.05$ considered statistically significant. The primary outcome variable (delivery room intubation or death) will represent a 2x2 cross table

and analysed with Pearson chi-square test. The secondary outcomes include Kaplan Meier analysis of time to intubation and comparisons of means for continuous variables. There are no predetermined subgroups. Subgroup analysis will be used to describe the population and to generate hypotheses.

Primary Outcome Measures: Delivery room intubation or death [Time Frame: 0-30 minutes]

Secondary Outcome Measures: Available at clinicaltrials.org

Adjustments during the trial

There were no adjustments in variables or plan.

Analysis after the trial

During the trial primary outcome and safety variables were independently monitored. After completion of the trial data was screened for outliers and incongruent values. Entries were corrected after contact with site PIs. All changes were tracked in eCRF log.

The primary outcome was analyzed using a logistic regression model adjusted for stratification variables. The model was also used for estimating an adjusted risk difference (reported in main text). The stratification variables were gestational age, antenatal steroid use, and center. Primary outcome was also investigated using a GGE multiple logistic regression model adjusted for stratification variables and multiple births (reported only in supplement).

Results from logistic regression:

GA >25 weeks OR 0.25 (95%CI 0.13-0.47, P=.000) with GA 24-25 weeks as reference.

Antenatal steroid use NS

One center with OR 9.0 (95%CI 2.5-32.2, P=.001)

Randomized to new system OR 0.53 (95%CI 0.30-0.94, P=.031)

Risk Difference -14.6%, CI -26.5% to -2.6%

Removal of centers with few cases (n<10 cases in 2: no antenatal steroids and one center) did not change the randomized system as important, OR 0.55 (95%CI 0.31-0.99, P=.047).

Adjusting also for multiple births using GEE:

GA >25 weeks OR 0.25 (95%CI 0.13-0.48, P=<0.0001) with GA 24-25 weeks as reference.

Antenatal steroid use NS

One center with OR 9.0 (95%CI 2.5-32.2, P=.0008)

Randomized to new system OR 0.53 (95%CI 0.30-0.94, P=.0309)

Risk Difference -14.6%, CI -26.5% to -2.6%

Student´s t-test and Mann-Whitney test were used as appropriate. Chi-square or Fisher's exact test was used to compare frequencies for tabulated variables. Relative risks with 95% CI was calculated. Due to limitations in SPSS ability to calculate risk differences these were performed in Excel. Deaths and intubations after 30 minutes were reported as delivery room outcome but not as primary outcome. The events in DR after 30 minutes were included in both the delivery room frequencies and the 72 hours follow-up.

Time to primary outcome (death or delivery room intubation) analysis had to be modified since the time when an infant left DR was not standardized. This was to avoid excluding events in patients that were transferred early to NICU or a late transfer resulting in more events in the DR. For example, a patient that was transferred and then directly intubated or died in NICU had to be reported transparently. Transfer to NICU was at age 10 to 180 minutes (n=242, median 25 min (IQR 36)). Nineteen patients stayed in the delivery room for more than two hours. This was due to logistical reasons in one center. These patients received NICU care until transfer. Events were defined as delivery room intubations and deaths (primary outcome) followed by mechanical ventilation or deaths in NICU. Intubations for INSURE or catheter delivery of surfactant in NICU (without mechanical ventilation) where not included. The Kaplan-Meier was analyzed using

logrank test at 30 minutes and 72 hours with a 0-30 min magnification provided by changing the scale of the X-axis. These were not statistically significant (p=.05 and p=0.07, not adjusted for multiple comparisons).

Background variables and other outcome variables were tabulated and analyzed as planned using Student's t-test, Chi-square and Fisher's exact test (Freeman-Halten). Non-tabulated data were tested for normality and compared using Mann-Whitney.

Primary outcome variable, death and mechanical ventilation, as well as safety variables were also reported with risk difference and 95% CI. As suggested in CONSORT risk ratios were also provided for the primary outcome.