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Short-term pulmonary and systemic effects of hydrocortisone initiated 7–14 days after birth in ventilated very preterm infants: a secondary analysis of a randomised controlled trial

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ABSTRACT

Objective Observational studies in preterm infants suggest that systemic hydrocortisone improves pulmonary condition but may also lead to systemic adverse effects. We report the short-term pulmonary and systemic effects of hydrocortisone initiated in the second week.

Design Randomised placebo-controlled trial.

Setting Dutch and Belgian neonatal intensive care units.

Patients Infants born <30 weeks' gestation and/or birth weight <1250 g, and ventilator dependent in the second week of life.

Intervention Infants were randomly assigned to a 22-day course of systemic hydrocortisone (cumulative dose 72.5 mg/kg; n=182) or placebo (n=190).

Main outcome measures Data on extubation, ventilator settings, glucose levels, and blood pressure were recorded daily and analysed during the first 7 days of treatment using linear mixed-effects models.

Results Infants in the hydrocortisone group (24.3%) failed extubation less often compared with placebo (38.6%, crude risk difference: -14.3% (95% CI: -23.4% to -4.8%)). The estimated difference in daily rate of change between hydrocortisone and placebo was -0.42 cmH₂O (95% CI: -0.48 to -0.36) for mean airway pressure, -0.02 (95% CI: -0.02 to -0.01) for fraction of inspired oxygen, -0.37 (95% CI: -0.44 to -0.30) for respiratory index, 0.14 mmol/L (95% CI: 0.08 to 0.21) for blood glucose levels and 0.83 mm Hg (95% CI: 0.58 to 1.09) for mean blood pressure.

Conclusions Systemic hydrocortisone initiated between 7 and 14 days after birth in ventilated preterm infants improves pulmonary condition, thereby facilitating weaning and extubation from invasive ventilation. The effects of hydrocortisone on blood glucose levels and blood pressure were mild and of limited clinical relevance.

Trial registration number Netherlands Trial Register (NTR2768; <https://www.trialregister.nl/trial/2640>) and European Union Clinical Trials Register (EudraCT, 2010-023777-19).

WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ Dexamethasone treatment in ventilator-dependent very preterm infants leads to a short-term improvement of lung function, and facilitates extubation, but also causes short-term adverse effects such as hyperglycaemia and hypertension.
- ⇒ Randomised data on short-term lung function changes and adverse systemic effects for hydrocortisone started after the first week are lacking.

WHAT THIS STUDY ADDS

- ⇒ This study shows that systemic hydrocortisone initiated between 7 and 14 days after birth in mechanically ventilated preterm infants improves pulmonary condition, and facilitates weaning and extubation.
- ⇒ Only mild elevations of blood glucose levels and blood pressure of hydrocortisone treatment were found in this study.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE AND/OR POLICY

- ⇒ Clinicians can use this information to determine their weaning and extubation strategy.

INTRODUCTION

Mechanically ventilated preterm infants are at high risk of developing bronchopulmonary dysplasia (BPD).¹ Pulmonary inflammation plays an important role in its pathogenesis.² For this reason, ventilated preterm infants are often treated with postnatal corticosteroids to improve lung function, facilitate weaning and extubation, and reduce the risk of developing BPD.^{3 4} Studies investigating the postnatal corticosteroid dexamethasone have shown positive effects on all these outcomes,^{5–7} but its use is also associated with short-term (hyperglycaemia, hypertension) and long-term (neurodevelopmental) adverse effects.^{3 4} Based on these concerns, the use of dexamethasone in preterm infants at risk of BPD

has dropped.⁸ Hydrocortisone is increasingly used as an alternative, although evidence from randomised controlled trials (RCTs) showing its efficacy and safety when initiated after the first week of life is limited.⁹

The SToP-BPD (Systemic Hydrocortisone To Prevent Bronchopulmonary Dysplasia in preterm infants) Study was the first large placebo-controlled RCT investigating the effect of systemic hydrocortisone treatment initiated in the second week of life in ventilator-dependent preterm infants. It showed that hydrocortisone does not reduce the risk of the combined outcome death or BPD at 36 weeks' postmenstrual age (PMA),¹⁰ and is not associated with the combined outcome death or neurodevelopmental impairment at 2 years' corrected age.¹¹ Despite its lack of efficacy on BPD, clinicians may still decide to administer hydrocortisone to improve lung function and facilitate extubation. We previously reported that hydrocortisone reduces extubation failure compared with placebo, but it is unclear if this is mediated by an improvement in lung function over time. The same is true for the short-term adverse effect on hyperglycaemia and hypertension. Therefore, we performed a secondary in-depth analysis of the short-term pulmonary and systemic effects of hydrocortisone treatment compared with placebo as observed in the SToP-BPD Study.

METHODS

Study design and participants

This double-blind, placebo-controlled RCT was performed in 16 neonatal intensive care units in the Netherlands and Belgium between 15 November 2011 and 23 December 2016; details are published elsewhere.^{10 12 13} In summary, infants born at a gestational age less than 30 weeks and/or with a birth weight less than 1250 g, who were ventilator dependent between day 7 and 14 of life, were randomly assigned to receive either hydrocortisone or placebo. Hydrocortisone sodium succinate was given to infants allocated to the intervention group in a tapered dosing scheme of 22 days with a cumulative dose of 72.5 mg/kg.

Study procedures and outcomes

Data on ventilator mode and settings were recorded at baseline and at the start of each day during the 22-day treatment course. Blood gas analyses, blood glucose levels and blood pressure measurements were performed as per local protocol and recorded if available for each day during the 22-day treatment course.

Outcomes of interest for this secondary analysis were the proportion of infants failing extubation and the median time to successful extubation. This analysis concerns an elaboration of our previously reported preliminary analysis of failure to extubate and duration of mechanical ventilation¹⁰; our previous analysis of failure to extubate was restricted to survivors at selected time points and currently a more strict definition of successful extubation is applied, that is, effectively remaining on non-invasive support for >72 hours.¹⁴ Data on extubation were collected over the 22-day period of study treatment and infants who died during this period were considered to have failed extubation.⁵ As daily lung function measurements were not feasible in this multicentre trial, we used the following indirect parameters of lung function: changes over time in mean airway pressure (MAWP) and respiratory index score (RI; defined as $\text{MAWP} \times \text{FiO}_2$) in infants supported by mechanical ventilation, and in the total population the fraction of inspired oxygen (FiO_2) and partial pressure of carbon dioxide (pCO_2). In addition, we assessed changes over time in blood pressure (mean, systolic and

diastolic) and blood glucose levels. The differences in rates of change in MAWP, FiO_2 , RI, pCO_2 , blood pressure and blood glucose levels were analysed during the first 7 days of treatment, as the hydrocortisone dosage was reduced after day 7 according to the tapered dosing scheme and the effect of hydrocortisone treatment on these outcomes is expected in the first days after start of treatment.

Statistical analysis

The sample size calculation for the trial was performed for the primary outcome death or BPD at 36 weeks' PMA, as previously reported.¹⁰ Although we preplanned these secondary analyses, no formal sample size calculation was performed. Baseline infant characteristics are presented as mean and SD, or median and IQR for continuous variables, or counts and percentages for categorical variables where appropriate.

Data analyses were intention-to-treat with all patients included in their randomly assigned treatment group regardless of protocol deviations or use of open-label corticosteroids. A crude absolute risk difference was calculated between the proportions of infants failing extubation after the study treatment course of 22 days, and a time-to-event analysis was performed using Kaplan-Meier survival curves with a log-rank test for the 22-day study treatment course; time-to-event was calculated as the time between randomisation and successful extubation or the end of the 22-day study treatment course (censoring event, in case of failure of extubation).

Rates of change per day during the first 7 days of treatment for the MAWP, FiO_2 , RI, pCO_2 , blood glucose levels and blood pressure were compared between treatment groups with linear mixed-effects models including time (days), treatment group (placebo, hydrocortisone), treatment group \times time interaction term, and adjusted for the stratification factor gestational age (<27 (reference group), ≥ 27 weeks) as fixed effects, and a random effect for the intercept. Maximum likelihood was used as the estimation method. Assumptions of linear mixed model analyses were checked using analysis of residuals. P values were calculated with the likelihood ratio test using the $-2 \log$ likelihoods of the models with and without treatment group \times time interaction.

Sensitivity analyses were performed to check the robustness of the analyses excluding infants who received no study medication ($n=3$; 1 hydrocortisone, 2 placebo) and infants who received any open-label corticosteroids during the study treatment course (proportion failing extubation) and during the first 7 days of treatment (pulmonary and systemic effects). Also a sensitivity analysis was performed for the pulmonary and systemic effects over the first 7 days of treatment in survivors only as data on these outcomes are missing for deceased infants.

For all treatment effect estimators, 95% CIs are presented; all analyses were performed using two-sided tests; $p < 0.05$ was regarded as statistically significant. No adjustments for multiple comparisons were made. Statistical analysis was performed in IBM SPSS Statistics for Windows, V.26.0 (IBM Corp).

RESULTS

In total, 372 infants were enrolled in the SToP-BPD Study of whom 182 infants were allocated to the hydrocortisone group and 190 infants to the placebo group; parents of one infant in the hydrocortisone group withdrew consent and this infant was excluded from all outcome analyses. Clinical characteristics at the time of randomisation were similar in both allocation groups, except for an average 65 g higher birth weight, a 0.4 higher RI

Table 1 Baseline clinical characteristics

| | Hydrocortisone (n=181) | Placebo (n=190) |
|--|---------------------------|--------------------|
| Infant characteristics | | |
| Gestational age, median (IQR), weeks | 25.4 (24.9–26.4) | 25.6 (24.7–26.4) |
| Birth weight, median (IQR), g | 775 (643–865) | 710 (629–810) |
| Male sex, no (%) | 95 (52.5) | 109 (57.4) |
| Small for gestational age, no (%) | 26 (14.4) | 38 (20.0) |
| Multiple birth, no (%) | 70 (38.7) | 54 (28.4) |
| Antenatal corticosteroids (any), no (%) | 158 (87.3) | 172 (90.5) |
| Ventilator settings at randomisation | | |
| High-frequency oscillatory ventilation, no (%) | 101 (55.8) | 90 (47.4) |
| Mean airway pressure, mean (SD) | 12.1 (2.3) | 11.9 (2.2) |
| Fraction of inspired oxygen, median (IQR) | 0.35 (0.30–0.45) | 0.34 (0.29–0.40) |
| Respiratory index, median (IQR)* | 4.3 (3.3–5.3) | 3.9 (3.1–5.0) |
| Partial pressure of carbon dioxide, mean (SD), kPa | 6.8 (1.3) | 7.0 (1.3) |
| Other parameters at randomisation | | |
| Mean blood pressure, mean (SD), mm Hg | 39 (10) | 38 (7) |
| Systolic blood pressure, mean (SD), mm Hg | 52 (12) | 52 (10) |
| Diastolic blood pressure, mean (SD), mm Hg | 29 (9) | 29 (8) |
| Blood glucose level, mean (SD), mmol/L | 6.9 (2.3) | 6.8 (2.5) |

*Respiratory index was defined as mean airway pressure×fraction of inspired oxygen. IQR, Interquartile range; SD, Standard deviation.

score and 10% more multiple births in the hydrocortisone group (table 1).

In one infant in the placebo group, data on extubation were missing. At the end of the 22-day treatment course, a significantly lower proportion of hydrocortisone-treated infants failed extubation compared with the placebo group (24.3% vs 38.6%, respectively; crude risk difference: -14.3% (95% CI: -23.4% to -4.8%); log-rank test $p < 0.001$; figure 1). For those infants successfully extubated after treatment initiation, the median time to extubation was 9 days (IQR: 5–19.5 days) in the hydrocortisone group and 15 days (IQR: 10–23 days) in the placebo group.

MAWP, FiO₂ and RI decreased significantly over the first 7 days of treatment in the hydrocortisone group compared with the placebo group with an estimated difference in rates of change between the hydrocortisone and placebo group of -0.42 cmH₂O (95% CI: -0.48 to -0.36) per day for MAWP

($p < 0.001$), -0.02 (95% CI: -0.02 to -0.01) per day for FiO₂ ($p < 0.001$) and -0.37 (95% CI: -0.44 to -0.30) per day for RI ($p < 0.001$) (figure 2A–C and table 2). Availability of blood gas analyses ranged from 98% of infants at the start of study treatment to 79% of infants on day 7 of treatment. A significant difference in daily rate of change was seen for the pCO₂ in the hydrocortisone-treated infants compared with the placebo group (estimated difference in rate of change: -0.04 kPa (95% CI: -0.08 to -0.003) per day; $p = 0.03$; figure 2D and table 2).

The rate of change in blood glucose level of the hydrocortisone-treated infants was significantly higher compared with the placebo group (estimated difference in rate of change: 0.14 mmol/L (95% CI: 0.08 to 0.21) per day; $p < 0.001$; figure 3A and table 2). In addition, during the first 7 days of treatment, the mean, systolic and diastolic blood pressure increased significantly more in the hydrocortisone group compared with the placebo group (estimated difference in rate of change: 0.83 mm Hg (95% CI: 0.58 to 1.09), 1.00 mm Hg (95% CI: 0.70 to 1.31), 0.86 mm Hg (95% CI: 0.60 to 1.12) per day, respectively; $p < 0.001$; figure 3B and table 2).

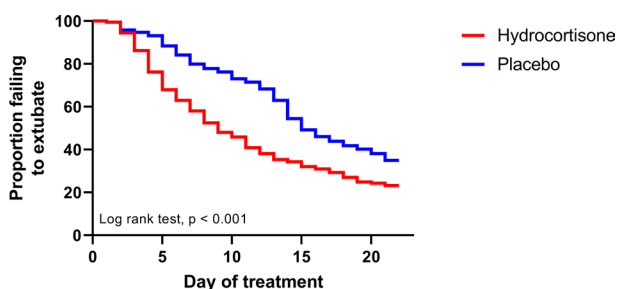
Sensitivity analyses in the surviving infants only and excluding infants who received no study medication or open-label corticosteroids yielded similar results (online supplemental figure 1, tables 1 and 2, online supplemental file 2).

DISCUSSION

This study shows that systemic hydrocortisone initiated between 7 and 14 days after birth in mechanically ventilated preterm infants born before 30 weeks' gestation improves lung function, assessed by the MAWP and oxygen need, and facilitates extubation. Furthermore, hydrocortisone treatment is associated with a higher daily rate of change in blood glucose level and more increase in blood pressures during the first 7 days of treatment.

The effect of hydrocortisone as compared with placebo on the course in lung function during the first 7 days of study treatment was estimated by the between-groups difference in daily rate of change in MAWP, FiO₂ and RI. Although the estimated beneficial effect of hydrocortisone on rate of change in MAWP and FiO₂ per day may appear modest, over a time period of a number of days it accumulates to a clinically relevant improvement, resulting in a higher rate of successful extubation and shorter time to extubation. Importantly, the faster weaning of ventilatory pressures in the hydrocortisone group compared with the placebo group was not accompanied by a clinically relevant difference in the course in pCO₂ between both groups. In addition, our study showed that the median time to extubation was 9 days in hydrocortisone-treated infants compared with 15 days in the placebo group. In line with recently published population-based observational studies, this reduction in the duration of mechanical ventilation did not result in a decrease of BPD incidence.^{15 16} However, shortening invasive ventilation by 6 days may have important implications as retrospective cohort studies have shown that each additional day of mechanical ventilation was negatively correlated with long-term neurodevelopmental impairment.^{17 18}

RCTs investigating prophylactic hydrocortisone treatment, started in the first week of life, to date, have not reported the impact on lung function parameters such as MAWP, FiO₂ and RI.^{19–23} The PREMILOC Study, investigating early low-dose hydrocortisone in preterm infants, reported a higher rate of extubated infants by day 7 of treatment in the hydrocortisone group (58%) compared with the placebo group (47%).¹⁹ This finding indirectly suggests that, in line with our study,



| Number failure to extubate | |
|----------------------------|--|
| Hydrocortisone | 181 139 ^a 87 ^b 62 ^c 45 ^d |
| Placebo | 189 177 ^a 144 ^b 103 ^c 77 ^d |

Figure 1 Kaplan-Meier analysis for proportion of infants failing to extubate over the full 22 days of treatment. ^aIncludes nine deaths in the hydrocortisone group and eight deaths in the placebo group. ^bIncludes four additional deaths in the hydrocortisone group and eight additional deaths in the placebo group. ^cIncludes two additional deaths in the hydrocortisone group and six additional deaths in the placebo group. ^dIncludes five additional deaths in the hydrocortisone group and three additional deaths in the placebo group.

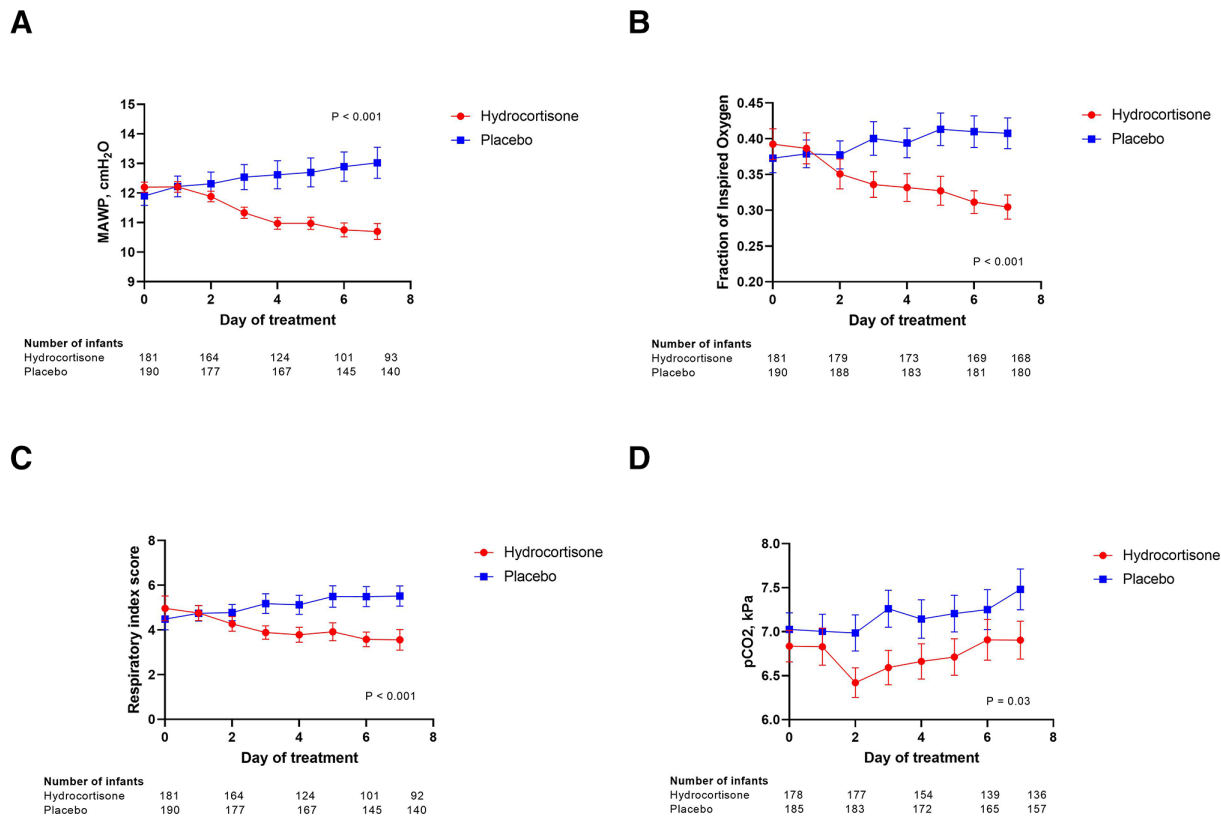


Figure 2 (A) Observed mean airway pressure (MAWP), (B) fraction of inspired oxygen, (C) respiratory index score and (D) partial pressure of carbon dioxide (pCO₂) during the first 7 days of treatment (observed mean daily values with 95% CIs).^a P values shown for the likelihood ratio test calculated using the $-2 \log$ likelihoods of the mixed models with and without treatment group \times time interaction.

prophylactic hydrocortisone also improves the pulmonary condition of these infants. However, comparison of these results with the current report should be done cautiously. In the early and prophylactic studies, hydrocortisone is started shortly after birth when ventilator-induced lung injury is still limited. In contrast, infants included in our study in the second week of life were at a higher risk of having a poorer pulmonary condition at the start of hydrocortisone treatment.

For the mostly investigated corticosteroid dexamethasone, several RCTs showed short-term lung function improvement as reflected by lower ventilator settings 48 hours after start of treatment and faster extubation.^{3 4 6 7 24} Our findings are in line with these studies, which strongly suggests that both dexamethasone and hydrocortisone have beneficial effects on short-term lung function in mechanically ventilated preterm infants. Since there are no RCTs comparing head-to-head hydrocortisone versus dexamethasone, it remains unknown which drug is superior in achieving these rapid improvements in pulmonary condition.

Other systemic outcome parameters, such as blood pressure and glucose levels, are also affected by corticosteroids. We found a significantly increase of blood glucose levels and blood pressure per day in hydrocortisone-treated infants. In this patient population at risk of hyperglycaemia, the observed higher glucose levels were in most cases relatively mild, as previously reported.¹⁰ The rate of hypertension, using predefined cut-off values depending on gestational age, was low and similar in both groups.¹⁰ Studies on prophylactic hydrocortisone and studies on prophylactic and targeted dexamethasone treatment showed a similar increase in blood glucose levels and blood pressure over time,^{5 25} and reported a significant increased risk for both hyperglycaemia and hypertension.^{3 4}

The primary goal of systemic corticosteroid treatment is to reduce the incidence of BPD at 36 weeks' PMA, and our previous report showed that hydrocortisone was not effective in reducing this outcome.¹⁰ However, corticosteroids are also administered to facilitate weaning and extubation from (protracted) invasive mechanical ventilation. Therefore, the results of this secondary analysis of the SToP-BPD Study have important clinical implications. This study shows that hydrocortisone will improve the pulmonary condition facilitating earlier weaning of MAWP and FiO₂. Furthermore, this pulmonary improvement leads to successful extubation in most infants at a median time point of 9 days. The relatively mild elevations of blood glucose levels and blood pressure do not seem to outweigh these beneficial effects on short-term lung function. Clinicians can use this information to determine their weaning and extubation strategy.

Limitations

Our study has a few limitations. First, after extubation, infants were supported by non-invasive respiratory support, and invasive MAWP was no longer measured. However, as the median time to successful extubation was 9 days in the hydrocortisone group, we do not expect that this limitation has hampered our findings on the MAWP and RI. Second, a relatively high proportion of infants in the placebo group (56.8%) was eventually treated with open-label hydrocortisone, which may have diluted a possible effect of hydrocortisone on the ventilator and oxygen requirements. The performed sensitivity analysis to explore possible bias by open-label corticosteroids seems reassuring as it yielded similar treatment effect for any of the outcome variables.

Table 2 Differences in change over time in pulmonary and systemic outcomes between hydrocortisone and placebo group in the intention-to-treat population, during the first 7 days of treatment*

| Outcomes | Estimated difference in rate of change per day (95% CI)†, hydrocortisone vs placebo | P value‡ |
|--|---|----------|
| Mean airway pressure (cmH ₂ O)§ | -0.42 (-0.48 to -0.36) | <0.001 |
| FiO ₂ | -0.02 (-0.02 to -0.01) | <0.001 |
| Respiratory index score | -0.37 (-0.44 to -0.30) | <0.001 |
| pCO ₂ (kPa)¶ | -0.04 (-0.08 to -0.003) | 0.03 |
| Blood glucose level (mmol/L)¶¶ | 0.14 (0.08 to 0.21) | <0.001 |
| Mean blood pressure (mm Hg) | 0.83 (0.58 to 1.09) | <0.001 |
| Systolic blood pressure (mm Hg) | 1.00 (0.70 to 1.31) | <0.001 |
| Diastolic blood pressure (mm Hg) | 0.86 (0.60 to 1.12) | <0.001 |

*Linear mixed models including time (days), treatment group (placebo, hydrocortisone), treatment group×time interaction and the stratification factor gestational age (<27, ≥27 weeks) as fixed factors. Reference groups are <27 weeks for gestational age and placebo for treatment group. Dependency of repeated measures was taken into account by including a random intercept for each patient and maximum likelihood was used as the estimation method.

†Estimated difference in linear rate of change per day (ie, difference in mean change in outcome variable per day), estimated by the regression coefficient of the treatment group×time interaction.

‡P values shown for the likelihood ratio test calculated using the -2 log likelihoods of the maximum likelihood mixed models with and without treatment group×time interaction.

§For infants supported with conventional mechanical ventilation and without a recorded mean airway pressure (MAWP), the MAWP was calculated using the following formula: [MAWP=(PIP-PEEP)×T_i/(T_i+T_e)+PEEP].²⁶ In this formula, PIP is the peak inspiratory pressure, PEEP is positive end-expiratory pressure, T_i is inspiratory time and T_e is expiratory time.

¶¶The units used for the collected blood glucose levels and pCO₂ values differ per centre, mg/dL or mmol/L for blood glucose level and mm Hg or kPa for pCO₂. To compare the blood glucose levels and pCO₂ values in the total population, the available blood glucose levels in mg/dL were converted to mmol/L and for the pCO₂ mm Hg was converted to kPa.

FiO₂, fraction of inspired oxygen; pCO₂, partial pressure of carbon dioxide.

CONCLUSION

Systemic hydrocortisone initiated between 7 and 14 days after birth in mechanically ventilated preterm infants born before 30 weeks' gestation significantly improves the pulmonary condition, thereby facilitating weaning and extubation from invasive mechanical ventilation. The effects of hydrocortisone on blood glucose levels and blood pressure were mild and of limited clinical relevance.

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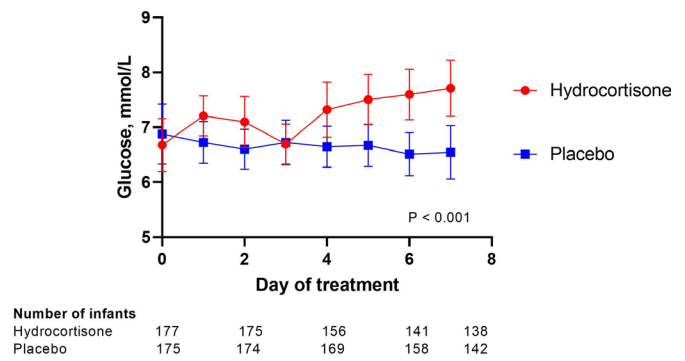
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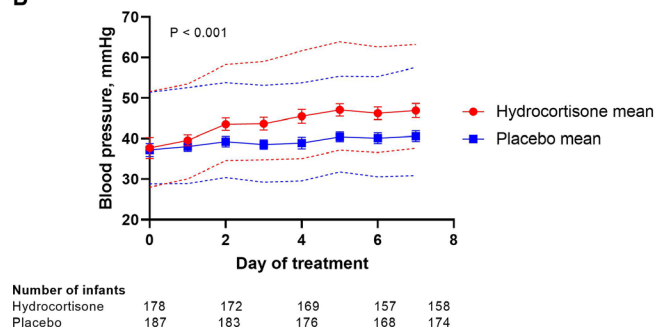


Figure 3 (A) Observed blood glucose levels and (B) blood pressure during the first 7 days of treatment (observed mean daily values with 95% CIs). For blood pressure, the upper dotted line represents the systolic blood pressure and the lower dotted line the diastolic blood pressure.^a ^aP values shown for the likelihood ratio test calculated using the -2 log likelihoods of the mixed models with and without treatment group×time interaction.

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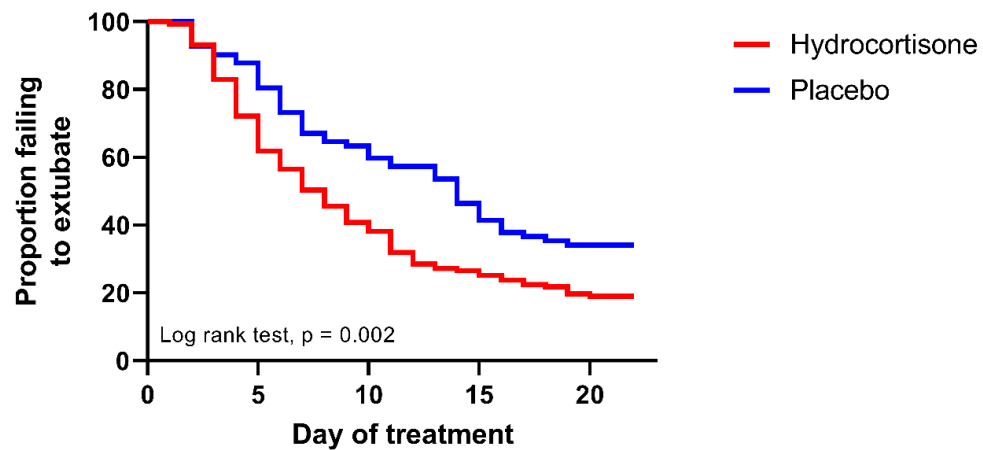
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Supplementary online content

eFigure 1. Kaplan-Meier analysis: for proportion of infants failing to extubate over the 22 days of treatment with exclusion of infants who received no dose of study medication (n=3) and infants who received any open-label corticosteroids during the study treatment course.



Number failure to extubate

| | | | | | |
|----------------|-----|------------------|-----------------|-----------------|-----------------|
| Hydrocortisone | 147 | 106 ^a | 60 ^b | 39 ^c | 29 ^d |
| Placebo | 82 | 72 ^a | 52 ^b | 38 ^c | 28 ^d |

^a Includes 5 deaths in the hydrocortisone group and 5 deaths in the placebo group.

^b Includes 3 additional deaths in the hydrocortisone group and 5 additional deaths in the placebo group.

^c Includes 2 additional deaths in the hydrocortisone group and 1 additional deaths in the placebo group.

^d Includes 3 additional deaths in the hydrocortisone group and 1 additional deaths in the placebo group.

eTable 1. Differences in change over time in pulmonary and systemic outcomes between hydrocortisone (n=169) and placebo (n=178) group in surviving infants, during the first 7 days of treatment. ^{a, b}

| Variables | Estimated difference in rate of change per day (95% CI) ^c , hydrocortisone vs. placebo | P value ^d |
|--|---|----------------------|
| Mean airway pressure (cm H ₂ O) | -0.42 (-0.48 to -0.36) | <0.001 |
| FiO ₂ | -0.02 (-0.02 to -0.01) | <0.001 |
| Respiratory Index score | -0.36 (-0.43 to -0.29) | <0.001 |
| pCO ₂ (kPa) | -0.04 (-0.08 to -0.004) | 0.03 |
| Blood glucose level (mmol/L) | 0.16 (0.09 to 0.22) | <0.001 |
| Mean blood pressure (mmHg) | 0.82 (0.57 to 1.08) | <0.001 |
| Systolic blood pressure (mmHg) | 0.99 (0.68 to 1.29) | <0.001 |
| Diastolic blood pressure (mmHg) | 0.85 (0.60 to 1.11) | <0.001 |

FiO₂=fraction of inspired oxygen, pCO₂=partial pressure of carbon dioxide, CI=confidence interval

^a Linear mixed model including time (days), treatment group (placebo, hydrocortisone), interaction time × treatment group and the stratification factor gestational age (<27, ≥ 27 weeks) as fixed factors. Reference groups are placebo for treatment group and <27 weeks for gestational age. Dependency of repeated measures was taken into account by including a random intercept for each patient and maximum likelihood was used as the estimation method.

^b Only infants surviving at 7 days of follow up analysed. Summary baseline characteristics of surviving infants were similar to those of the respective intention-to-treat treatment groups with no clinical differences in baseline characteristics between surviving HC and placebo treatment groups.

^c Estimated difference in linear rate of change per day (i.e. difference in mean change in the outcome variable per day), estimated by the regression coefficient of the treatment group × time interaction.

^d P-value for the likelihood ratio test calculated using the -2 log likelihoods of the maximum likelihood mixed models with and without treatment group × time interaction.

eTable 2. Differences in change over time in pulmonary and systemic outcomes between hydrocortisone (n=171) and placebo (n=141) group in the population excluding infants who received no dose of study medication (n=3) and infants who received any open-label corticosteroids, during the first 7 days of treatment. ^{a, b}

| Variables | Estimated difference in rate of change per day (95% CI) ^c , hydrocortisone vs. placebo | P value ^d |
|--|---|----------------------|
| Mean airway pressure (cm H ₂ O) | -0.42 (-0.48 to -0.35) | <0.001 |
| FiO ₂ | -0.02 (-0.02 to -0.01) | <0.001 |
| Respiratory Index score | -0.36 (-0.42 to -0.29) | <0.001 |
| pCO ₂ (kPa) | -0.07 (-0.11 to -0.03) | 0.001 |
| Blood glucose level (mmol/L) | 0.17 (0.09 to 0.24) | <0.001 |
| Mean blood pressure (mmHg) | 0.99 (0.71 to 1.27) | <0.001 |
| Systolic blood pressure (mmHg) | 1.24 (0.91 to 1.57) | <0.001 |
| Diastolic blood pressure (mmHg) | 0.91 (0.63 to 1.19) | <0.001 |

FiO₂=fraction of inspired oxygen, pCO₂=partial pressure of carbon dioxide, CI=confidence interval

^a Linear mixed model including time (days), treatment group (placebo, hydrocortisone), interaction time × treatment group and the stratification factor gestational age (<27, ≥ 27 weeks) as fixed factors. Reference groups are <27 weeks for gestational age and placebo for treatment group. Dependency of repeated measures was taken into account by including a random intercept for each patient and maximum likelihood was used as the estimation method.

^b Infants who received no dose of study medication (n=3) and infants who received open-label corticosteroids were excluded from this analysis. Summary baseline characteristics of infants with no study medication and without open-label corticosteroids were similar to those of the respective intention-to-treat treatment groups with no clinical differences in baseline characteristics between HC and placebo treatment groups in the subpopulation without open-label corticosteroids during the first seven days of study treatment.

^c Estimated difference in linear rate of change per day (i.e. difference in mean change in outcome variable per day), estimated by the regression coefficient of the treatment group × time interaction.

^d P-value for the likelihood ratio test calculated using the -2 log likelihoods of the maximum likelihood mixed models with and without treatment group × time interaction.

Original protocol and amendments STOP-BPD study

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In this document we have collected all versions of the STOP-BPD study protocol as submitted to the Ethics Committee of the Academic Medical Center in Amsterdam.

Version 1 is the original protocol submitted to the Ethics Committee

Version 2 is the revised version based on the comments of the Ethics Committee on the first submission.

Versions 3-5 contain small amendment changes that were submitted and accepted by the Ethics Committee.

All changes in the protocol versions are indicated by *Italic font*.

43 PROTOCOL

44 **Systemic Hydrocortisone To Prevent Bronchopulmonary Dysplasia in preterm**45 **infants: the SToP-BPD study**46 **A multicenter randomised placebo controlled trial**

| | |
|-------------------------------|---|
| Protocol ID | Systemic Hydrocortisone To Prevent Bronchopulmonary Dysplasia in preterm infants: the SToP-BPD study |
| Short title | SToP-BPD Study |
| Version | 1 |
| Date | 18 november 2010 |
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112 **LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS**

113

| | | |
|-----|---------|--|
| 114 | ARR | Absolute Risk Reduction |
| 115 | BPD | BronchoPulmonary Dysplasia |
| 116 | BW | Birth Weight |
| 117 | CDP | Continuous Distension Pressure |
| 118 | CGA | Corrected Gestational Age |
| 119 | CP | Cerebral Palsy |
| 120 | DNRN | Dutch Neonatal Research Netwerk; in Dutch: Nederlands Neonataal |
| 121 | | Research Netwerk (NNRN) |
| 122 | DSMB | Data Safety Monitoring Board |
| 123 | ESEMC | External Safety and Efficacy Monitoring Committee |
| 124 | GA | Gestational Age |
| 125 | HFO | High Frequency Oscillation |
| 126 | IMP | Investigational Medicinal Product |
| 127 | IVH | IntraVentricular Haemorrhage |
| 128 | MAwP | Mean Airway Pressure |
| 129 | METC | Medical research ethics committee (MREC); in Dutch: Medisch |
| 130 | | Ethische Toetsing Commissie |
| 131 | MRI | Magnetic Resonance Imaging |
| 132 | NEC | Necrotising EnteroColitis |
| 133 | NICU | Neonatal Intensive Care Unit |
| 134 | NICHD | National Institutes for Child Health and Human Development |
| 135 | NNT | Number Needed to Treat |
| 136 | NVK | Dutch Society of Pediatricians; in Dutch: Nederlandse Vereniging voor |
| 137 | | Kindergeneeskunde |
| 138 | PDA | Persistent Ductus Arteriosus |
| 139 | PMA | PostMenstrual Age |
| 140 | PNA | PostNatal Age |
| 141 | PVL | PeriVentricular Leucomalacia |
| 142 | RCT | Randomised Controlled Trial |
| 143 | RI | Respiratory Index |
| 144 | SAE | Serious Adverse Event |
| 145 | SD | Standard Deviation |
| 146 | Sponsor | The sponsor is the party that commissions the organisation of |
| 147 | | performance of the research, for example a pharmaceutical company, |
| 148 | | academic hospital, scientific organisation or investigator. A party that |
| 149 | | provides funding for a study but does not commission it is not |
| 150 | | regarded as the sponsor, but referred to as a subsidising party. |
| 151 | VLBW | Very Low Birth Weight |
| 152 | WMO | Medical Research Involving Human Subjects Act; in Dutch: Wet |
| 153 | | Medisch-wetenschappelijk Onderzoek met Mensen |
| 154 | | |

155

156 **SUMMARY**

157 **Background:** Randomised controlled trials (RCTs) have shown that treatment of chronically
158 ventilated preterm infants after the first week of life with dexamethasone reduces the
159 incidence of bronchopulmonary dysplasia (BPD). However, there are concerns that its use
160 may increase the risk of adverse neurodevelopmental outcome. Hydrocortisone has been
161 suggested as an alternative therapy. So far no RCT has investigated its efficacy when
162 administered after the first week of life to ventilated preterm infants.

163 **Objective:** To establish the efficacy of hydrocortisone given after one week of life to reduce
164 the incidence of the combined outcome death or BPD in chronically ventilated preterm
165 infants.

166 **Study design:** Randomised double blind placebo controlled multicenter study.

167 **Study population:** Very low birth weight infants (GA<30weeks and/or BW<1250grams),
168 ventilator dependent at a postnatal age of 7 – 14 days.

169 **Intervention:** Administration of hydrocortisone or placebo during a 22 day tapering
170 schedule.

171 **Outcome parameters:** Primary outcome measure is survival free of BPD at 36 weeks
172 postmenstrual age (PMA). Secondary outcomes are short term effects on the pulmonary
173 condition, adverse effects during hospitalization, and long-term neurodevelopmental
174 sequelae assessed at 2 years corrected gestational age (CGA).

175 **Burden, benefit and risks associated with participation; group relatedness:**

176 Burden: All infants participating in (either treatment arm of) the study are subjected to
177 routine neonatal intensive care. The administration of the study intervention itself
178 (hydrocortisone or placebo administration) does not pose an extra burden on the patients.
179 This study does not require extra investigations or interventions.

180 Benefit and risks: Hydrocortisone may facilitate extubation and thereby reduce the total
181 duration of mechanical ventilation. In addition, hydrocortisone may reduce the incidence of
182 BPD. Both these beneficial effects may improve neurodevelopmental outcome. On the other
183 hand, use of hydrocortisone may increase the risk for hyperglycemia, hypertension, systemic
184 infection, gastrointestinal perforation and a delay in neurodevelopment. However,
185 gastrointestinal perforation and delayed neurodevelopment have only been reported in
186 studies administering corticosteroids in the first week of life and/or in combination with
187 other medication. In this study the risk of gastrointestinal perforation and delayed
188 neurodevelopment may be reduced because hydrocortisone will be administered after the
189 first week of life and will not be combined with other drugs that are known to increase the
190 risk for these adverse effects. Infants assigned to the placebo group will not benefit from the
191 aforementioned possible beneficial effects nor be subjected to the possible adverse effect of
192 hydrocortisone.

193 Group relatedness: BPD is a complication occurring exclusively in preterm infants. Any
194 intervention aiming to reduce the risk of this complication therefore needs to be studied in
195 this specific population at risk.

196 **1. BACKGROUND**

197 Bronchopulmonary dysplasia (BPD) is the most common complication of premature birth,
198 with a reported incidence of 8% to 35%.^{1,2} BPD is characterized by chronic respiratory
199 distress, the need for prolonged respiratory support, an increased risk of recurrent
200 pulmonary infections, airway hyperreactivity during the first years of life³ and life-long
201 alterations in lung function.⁴⁻⁶ Patients with established BPD have high rates of readmissions
202 and utilization of health services resulting in tremendous societal costs compared to children
203 without BPD.⁷⁻⁹ Furthermore, BPD is considered an important risk factor for adverse
204 neurodevelopmental outcome after premature birth¹⁰⁻¹⁴ with life-long economic and social
205 consequences.¹⁵⁻¹⁸

206

207 In addition to direct mechanical injury, caused by artificial ventilation and oxygen toxicity,
208 pulmonary inflammation has been identified as an important mediator in the development
209 of BPD.¹⁹⁻²¹ This is the rationale for treating patients with glucocorticoids, a well known anti-
210 inflammatory agent. Randomised controlled trials (RCTs) summarized in several systematic
211 reviews have shown that postnatal systemic glucocorticoids, mainly dexamethasone, reduce
212 the risk of the combined outcome death or BPD in ventilated preterm infants.²²⁻²⁴

213 Furthermore, systemic glucocorticoids seem to be most effective when administered in a
214 time frame of 7 to 14 days postnatal age, the so-called moderately early treatment
215 onset.^{25,26} However, initiating dexamethasone treatment in the first days of life seems to be
216 associated with an increased the risk of cerebral palsy (CP). Although this complication has
217 not been reported by RCTs investigating dexamethasone treatment initiated after the first
218 week of life, these alarming reports have resulted in a general concern on the use of
219 dexamethasone in preterm infants.²⁷⁻²⁹ Based on this concern, the American Academy of

220 Pediatrics, Canadian Paediatric Society, and the European Association of Perinatal Medicine
221 have stated that clinical trials should be performed to investigate the use of alternative anti-
222 inflammatory glucocorticoids, such as the less potent glucocorticoid hydrocortisone.^{30,31}
223
224 Despite the ongoing concerns on their use, systemic glucocorticoids are still used in
225 approximately 10% of the preterm infants at risk for BPD.³²⁻³⁴ Dexamethasone is still the
226 most widely used glucocorticoid drug, but its dose has been significantly reduced and
227 administration is often postponed until the 3rd or 4th week of life.²⁷
228
229 As an alternative, many clinicians have started to use hydrocortisone. Animal data suggest
230 that hydrocortisone has a less detrimental effect on the brain than dexamethasone.³⁵
231 However, no placebo controlled RCT has investigated the use of hydrocortisone after the
232 first week in life in ventilator dependent preterm infants.³⁶ Six RCTs investigating a low
233 hydrocortisone dose started within < 72 hours after birth (early treatment) failed to show a
234 clear reduction in the incidence of BPD.³⁷⁻⁴² Only one of these trials reported long-term
235 follow-up, showing no differences in adverse neurodevelopmental sequelae.⁴³ These
236 findings are supported by several historical cohort studies, showing no increased risk of
237 adverse neurodevelopmental outcome in hydrocortisone treated infants.⁴⁴⁻⁴⁶
238
239 In most Dutch Neonatal Intensive Care Units (NICUs) preterm infants who are ventilator-
240 dependent in the second week of life are no longer treated with glucocorticoids. Infants are
241 kept on the ventilator allowing spontaneous recovery of lung function over time, sometimes
242 supported by other interventions, such as diuretics and inhalation therapy. With this
243 approach, some infants can be successfully weaned and extubated. Only those infants that

244 remain ventilator dependent after 3-4 weeks are treated with glucocorticoids, with the
245 primary objective to wean and extubate.

246 Although this approach will undoubtedly result in successful extubation of most infants with
247 the lowest possible use of glucocorticoids, the questions remains if this is also the best
248 strategy in reducing the incidence of BPD in preterm infants ventilated after 7 days of life.

249 This questions seems justified and relevant because BPD, and not failure to extubate, is
250 associated with adverse medium- and long-term outcome. This is the main reason why the
251 primary outcome of this study is death or BPD and not failure to extubate.

252

253 The NICU at the University Medical Center Utrecht, has historically used hydrocortisone for
254 chronically ventilated preterm infants. Retrospective studies seem to indicate that
255 hydrocortisone is effective in reducing BPD, without causing serious adverse effects.

256 However, these findings need to be confirmed or refuted by a large randomized placebo
257 controlled trial. Despite the absence of randomized evidence, three out of the 10 Dutch
258 NICUs switched from dexamethasone to hydrocortisone. This diversity in treatment between
259 NICUs is undesirable and has also been debated in the public press.⁴⁷ As a first step to
260 resolve this diversity in treatment, all 10 Dutch NICUs have indicated that a RCT comparing
261 hydrocortisone with placebo is urgently needed, an initiative that is also supported by the
262 Dutch Society of Pediatricians (NVK), giving such a trial top priority. Since the NICUs which
263 already use hydrocortisone are reluctant or refuse to prescribe dexamethasone as trial
264 medication, a RCT comparing dexamethasone versus hydrocortisone is not possible.

265

266 The optimal dose of hydrocortisone is currently unknown. However, the NICU in Utrecht has
267 been using a fixed hydrocortisone treatment regimen for several decades now and this

268 regimen has also been adopted by the other Dutch NICUs using hydrocortisone.
269 Retrospective studies strongly suggest that this is a safe dose, because it was not associated
270 with an increased risk of adverse neurological outcome.^{45,48} Comparing hydrocortisone
271 treated patients with dexamethasone treated patients in other NICUs showed no difference
272 in the incidence of BPD, suggesting that this dose is equally effective in reducing BPD.⁴⁸
273 Based on these findings and current clinical practice, we decided to adopt the dosing
274 regimen from Utrecht for this study.
275 Comparison of hydrocortisone to a placebo seems warranted because many NICUs
276 nowadays try to avoid the use of glucocorticoids as much as possible. If patients do get
277 treatment, this is usually late in the course of their disease. Although open label use of
278 glucocorticoids is strongly discouraged in this study, its use is not prohibited.
279 Although based on the above, the *extra* risks for the patients in this study are probably
280 limited, a data monitoring committee will closely monitor any possible adverse effects and
281 risks, as also explained in paragraph 8.4.

282

283 **2. OBJECTIVE**

284 To investigate if hydrocortisone is safe and effective in reducing the incidence of the
285 combined outcome death or BPD at 36 weeks PMA in chronically ventilated preterm infants,
286 as compared to placebo. This study **does not** aim to successfully extubate ventilator-
287 dependent preterm infants with the lowest possible use of glucocorticoids (i.e.
288 hydrocortisone), but to use glucocorticoids as an early intervention (7-14 d after birth) to
289 reduce the risk of death or BPD in these ventilator-dependent preterm infants. From this
290 point of view the treatment strategy is fundamentally different from what is currently used
291 in daily clinical practice.

292

293 **3. STUDY DESIGN**

294 Multicenter randomised double-blind placebo-controlled trial.

295

296 **4. STUDY POPULATION**

297 **4.1 Population eligibility**

298 Ventilated VLBW infants at high risk for BPD treated in a level III NICU

299

300 **4.2 Inclusion criteria**

301 Preterm infants with:

- 302 - a gestational age < 30 wks and/or birth weight < 1250 g
- 303 - ventilator dependent at 7-14 days PNA
- 304 - a respiratory index (MAwP x FiO₂) of ≥ 3.5 for more than 12 h/day for at least 48
- 305 hours, ensuring normal oxygen saturation (86-94%) and pCO₂ values in premature
- 306 infants (5.0-7.0 kPa).

307

308 **4.3 Exclusion criteria**

- 309 - chromosomal defects (e.g. trisomy 13, 18, 21)
- 310 - major congenital malformations that:
- 311 ○ compromise lung function (e.g. surfactant protein deficiencies, congenital
- 312 diaphragmatic hernia)
- 313 ○ result in chronic ventilation (e.g. Pierre Robin sequence)
- 314 ○ increase the risk of death or adverse neurodevelopmental outcome
- 315 (congenital cerebral malformations)

316 - Use of dexamethasone or hydrocortisone for the sole purpose of improving lung
317 function and respiratory status

318

319 Although (suspected or proven) sepsis, pneumonia, necrotizing enterocolitis (NEC) and
320 patent ductus arteriosus (PDA) are well-known causes of respiratory failure, these diagnoses
321 are known to be independent risk factors for developing BPD. Therefore, these diagnoses are
322 not considered to be exclusion criteria. The following should be taken into consideration:

323 1. In ventilator-dependent cases of sepsis and pneumonia the attending physician may
324 start antibiotics and await the effect on respiratory drive/ pulmonary status for 48
325 hours. If the patient meets the inclusion criteria after 48 h, he/she is eligible for
326 inclusion.

327 2. It is strongly recommended to screen all ventilator-dependent preterm infants for a
328 PDA at 5 days PNA. In case of a hemodynamically important PDA, medical intervention
329 according to local protocols should be started as soon as possible. Ibuprofen or
330 indomethacin treatment should not be combined with glucocorticoids, because it has
331 been suggested that this combination will increase the risk of intestinal perforation.
332 If, subsequently, the patient can't be extubated following medical treatment or
333 requires surgical PDA closure, he/she should be included in the study - provided that
334 all inclusion criteria are met.

335 3. If the physician considers extubation not an option because of the general condition
336 of the infant (e.g. NEC with severe hemodynamic instability and severe abdominal
337 distension) inclusion in the study can be postponed until the maximum of 14 days
338 PNA.

339

340 **4.4 Sample size calculation**

341 The primary outcome parameter is BPD free survival at 36 weeks PMA. The a priori risk of
342 death or BPD in preterm infants less than 30 weeks gestation and ventilated in the second
343 week of life is estimated at 60 – 70%. The meta-analysis on moderately early
344 dexamethasone treatment estimated an absolute risk reduction (ARR) of 25% (NNT=4)
345 compared with placebo.²⁴ However, there are no data currently available on the efficacy of
346 hydrocortisone and the suggested cumulative dose in the present study is considerably
347 lower compared to previously used dexamethasone doses. Since the shown efficacy of
348 dexamethasone is dependent on the used doses in these trials²⁶, we would propose a more
349 conservative approach, defining an ARR of 15% or more (NNT=7) as clinically relevant. With
350 an estimated *a priori* risk for death or BPD at 36 weeks PMA of 60%, a type I error of 5% (2
351 tailed) and a power of 80% the number of patients to be included in each treatment arm
352 would be 175 (total 350). Anticipating a 10% drop out of randomized patients, 200 patients
353 need to be included in each treatment arm (total 400). Based on a retrospective analysis of
354 ventilated preterm infants at day 7 of life in the majority of Dutch NICUs we expect a total of
355 200 eligible patients each year. With an estimated inclusion rate of 66% of eligible patients
356 and an inclusion period of 3 years, a total of 400 patients should be included in the study.
357 For sample size calculation we used Nquery (Statistical Solutions Ltd., Cork, Ireland).

358

359 **5. METHODS**

360 **5.1 Randomisation, blinding and treatment allocation**

361 Written informed consent has to be obtained from either parents or care-givers prior to
362 randomisation. In case of ventilator dependency after day 7 of life with a suspected diagnosis
363 of developing BPD, parents receive the study information as soon as possible allowing them

364 sufficient time to consider participation. The actual decision to include the patient in the trial
365 should be made between day 7 and 14 PNA. The first dose of study medication should be
366 administered within 72 hours after this decision. Randomization will be centrally controlled
367 and web-based using a computer program designed for this study. This trial will be protected
368 from selection bias by using concealed, stratified and blocked randomisation.

369

370 Randomisation will be stratified per center and according to gestational age stratum (Stratum
371 A: 24-26 weeks; Stratum B: 26-28 weeks; Stratum C: >28 weeks), in order to achieve an
372 equal distribution in both treatment arms. The allocation ratio will be 1:1 with block
373 randomisation using variable block sizes. Multiple birth infants will be randomised
374 independently, unless the parents or caretakers explicitly demand that the siblings should be
375 treated according to the same treatment arm. An automated mechanism to perform twin
376 randomisation is in place.

377 The infants' parents and all members of the medical team, including investigators, remain
378 blinded to group assignment throughout the study.

379

380 Patient characteristics, including gestational age, birth weight and respiratory status, will be
381 collected from all eligible infants that are not included in the study. In addition, we will
382 collect data on why the patients were not included. With this information we will assess
383 possible bias in patient inclusion.

384

385 **5.2 Withdrawal of individual subjects**

386 Parents or caregivers can leave the study at any time for any reason if they wish to do so
387 without any consequences. The investigator/attending physician can decide to withdraw a
388 subject from the study in case of prespecified treatment failure (see section 6.1.2).

389

390 **5.3 Replacement of individual subjects after withdrawal**

391 The number of withdrawn patients not marked as prespecified treatment failure (see section
392 6.1.2) will be replaced.

393

394 **5.4 Follow-up of subjects withdrawn from treatment**

395 Subjects withdrawn from the study will be treated according to the standard of care, including
396 neurodevelopmental outcome assessment at the outpatient clinic.

397

398 **5.5 Premature termination of the trial**

399 An independent *Data Safety Monitoring Board* will monitor the study on safety aspects (see
400 section 8.4) and if necessary recommend termination of the study.

401

402 **6. TREATMENT OF SUBJECTS**

403 **6.1. Therapeutic details**

404 6.1.1 Preparation of the trial medication: Both hydrocortisone and placebo will be prepared
405 according to GMP guidelines. In close collaboration with the AMC pharmacy (Dr. M.
406 Kemper) we are currently investigating the best way of preparing and supplying the drugs to
407 the participating centers. We will provide this information at a later date. The infants of the
408 hydrocortisone group will receive hemisuccinate hydrocortisone 5mg/kg/day Q.I.D for 7
409 days, followed by 3.75 mg/kg/day T.I.D. for 5 days, subsequently lowering the frequency by
410 one dose every 5 day. This leads to a total duration of therapy of 22 days and a cumulative
411 dose of 72.5 mg/kg hydrocortisone (see appendix 1). The infants in the control group receive
412 saline placebo for the entire 22-day period in the same frequency as the hydrocortisone group.

413 Both saline and hydrocortisone schedules will be calculated according to weight on the day of
414 randomisation and not adjusted to the actual weight during the tapering schedule.

415

416 6.1.2 Stop criteria during study protocol medication (treatment failure): In case of life
417 threatening deterioration of the pulmonary condition, the attending physician may decide to
418 start open label corticosteroids therapy in an attempt to improve the pulmonary condition. At
419 that point in time the study medication is stopped and the patient will be recorded as
420 “treatment failure”. In case of treatment failure the following data will be collected: timing of
421 treatment failure, ventilatory support and settings, type of open label medication, starting date,
422 cumulative dose and duration of rescue therapy. The patients will be followed as all other
423 patients until the clinical endpoints occur or until end of follow up.

424

425 6.1.3 Late rescue therapy outside study protocol (late rescue glucocorticoids): Patients still on
426 mechanical ventilation after completion of the study medication, i.e. day 22, may be treated
427 with open label corticosteroids. Data on type of open label medication, the starting date,
428 cumulative dose and duration of rescue therapy are collected.

429

430 6.1.4 Anti-hypotensive therapy: In case of persistent hypotension, not (sufficiently)
431 responding to first line treatment with intravascular volume expansion and inotropes
432 (dopamine and/or dobutamine) the use of hydrocortisone. Treatment for hypotension will not
433 be considered as treatment failure. Data on timing, dose and duration will be collected.

434

435 **6.2. Use of co-intervention**

436 All randomized patients will be treated according to the guidelines of the individual NICUs.

437 All participating NICUs explore treatable causes of ventilator dependency during the first

438 week of life, such as patent ductus arteriosus, sepsis and pneumonia as much as possible and
439 to treat these according to the department protocol. Although all of these conditions can be an
440 alternative cause of respiratory failure, they are known risk factors for developing BPD and
441 therefore are not considered exclusion criteria.

442

443 This trial will monitor the prognostically important co-interventions and conditions, as
444 described in section 7.2.

445

446 **6.3. Endpoints**

447 6.3.1. Primary endpoint: the dichotomous variable *BPD free survival at 36 weeks PMA*. BPD
448 at 36 weeks PMA will be assessed according to the NIHCHD Consensus Statement defining
449 normal oxygen saturation as 86%-94%. The severity of the BPD will be assessed as proposed
450 by Jobe et.al.²¹, since the severity of BPD has a high association with neurodevelopmental
451 sequelae.¹² In case of supplemental oxygen delivery >21% and < 30% or low flow at 36 weeks
452 PMA, the oxygen reduction test as described by Walsh et.al.^{21,49,50} should be preformed. A
453 positive oxygen reduction test has a high correlation with the risk on discharge home with
454 oxygen, the length of hospital stay, and pulmonary morbidity requiring hospital readmission
455 during the first year of life. For practical guidance on the use of the oxygen reduction test
456 please go to appendix 2.

457

458 6.3.2. Secondary endpoints:

- 459 • treatment failure as defined in section 6.1.2
- 460 • mortality at 28 days PNA, 36 weeks PMA and at hospital discharge
- 461 • BPD at 28 days

- 462 • failure to extubate 3, 7, 14 and 21 days after initiating therapy
- 463 • duration of mechanical ventilation
- 464 • use of “rescue treatment” with hydrocortisone outside the study protocol
- 465 • total time on supplemental oxygen
- 466 • length of hospital stay
- 467 • incidence of hypertension, defined as systolic blood pressure > 2SD of standardized
- 468 values used in the department
- 469 • hyperglycemia requiring the use of insulin therapy
- 470 • nosocomial infection, like sepsis, meningitis and pneumonia
- 471 • hemodynamic significant patent ductus arteriosus for which medical intervention or
- 472 surgical ligation is needed
- 473 • necrotising enterocolitis (NEC), diagnosed at surgery, autopsy or by radiographic
- 474 finding of pneumatosis intestinalis or hepatobiliary gas (Bell stage II)
- 475 • gastrointestinal bleeding
- 476 • isolated gastrointestinal perforation diagnosed on abdominal radiography
- 477 • intraventricular haemorrhage (IVH) and/or periventricular leucomalacia (PVL),
- 478 including grading on cerebral ultrasonography according to protocol defined by Ment
- 479 et.al.⁵¹
- 480 • retinopathy of prematurity, including grading following international classification⁵²
- 481 • weight gain, head circumference and length gain at 36 weeks PMA
- 482 • long-term health and neurodevelopmental sequelae, assessed at 2 years CGA:
 - 483 ○ readmissions since first discharge home
 - 484 ○ weight, length and head circumference at 24 months c.a.

- 485 ○ Bayley Scales of Infant Development III, Mental Developmental Index and
486 Psychomotor Developmental Index
- 487 ○ cerebral palsy and severity of cerebral palsy using gross motor function
488 classification system
- 489 ○ hearing loss requiring hearing aids
- 490 ○ blindness
- 491 ○ behavioural problems (child behaviour checklist)

492

493 All primary and secondary endpoints are measured as part of standard usual care in the
494 Netherlands and will be derived from the charts of the patients by the investigators.

495

496 **7. DATA COLLECTION AND STATISTICAL ANALYSIS**

497 **7.1 Baseline characteristics**

498 Baseline characteristics are collected prior to inclusion and randomization with respect to the
499 following baseline characteristics: demographic details and patient characteristics, such as
500 gestational age, small for gestational age, antenatal problems, antenatal steroids, surfactant
501 therapy, mode of delivery, resuscitation details, Apgar scores, presence of IVH/PVL, and
502 occurrence of PDA. Base line characteristics on ventilator settings, gas exchange will be
503 collected on day of randomization.

504

505 **7.2 Co-interventions**

506 Timing, dose and duration of all co-interventions, such as methylxanthines, diuretics,
507 bronchodilators/inhalation corticosteroids and inhaled nitric oxide, as well as the ventilation
508 mode with the ventilator settings will be recorded and analyzed.

509

510 **7.3 Statistical analysis**

511 Normally distributed data will be presented as mean \pm standard deviations, not-normally
512 distributed data as medians and (interquartile) ranges. Categorical data will be analysed
513 using the Chi-square test. Continuous data will be analysed using the Student's *t* test or
514 Mann-Whitney test as appropriate. Both intention-to-treat and per-protocol analysis will be
515 employed. The effect of hydrocortisone on the primary outcome death or BPD will be
516 assessed by multi-variable logistic regression analysis including possible confounders.
517 Statistical significance is set at $p < 0.05$.

518

519 **8. SAFETY REPORTING**

520 **8.1 Section 10 WMO (Wet Medisch-wetenschappelijk Onderzoek met Mensen)**

521 In accordance to section 10, subsection 1, of the Dutch WMO, the investigator will inform the
522 subjects and the reviewing accredited METC (*Medisch Ethische Toetsingscommissie*) if
523 anything occurs, on the basis of which it appears that the disadvantages of participation may
524 be significantly greater than was foreseen in the research proposal. The study will be
525 suspended pending further review by the accredited METC, except insofar as suspension
526 would jeopardise the subjects' health. The investigator will take care that all subjects are kept
527 informed.

528

529 **8.2 Adverse and serious adverse events (SAE)**

530 Adverse events are defined as any undesirable experience occurring to a subject during a
531 clinical trial, whether or not considered related to the investigational drug. All adverse
532 events reported spontaneously by the subject's parents or caregivers or observed by the

533 investigator or his staff will be recorded. A **serious adverse event** is any untoward medical
534 occurrence or effect that at any dose
535 - results in death;
536 - is life threatening (at the time of the event);
537 - requires hospitalization or prolongation of existing inpatients' hospitalization;
538 - results in persistent or significant disability or incapacity;
539 - is a congenital anomaly or birth defect (not applicable in this trial);
540 - is a new event of the trial likely to affect the safety of the subjects, such as an unexpected
541 outcome of an adverse reaction, lack of efficacy of an IMP used for the treatment of a life
542 threatening disease, major safety finding from a newly completed animal study, etc.
543 All SAEs will be reported to the Data Monitoring Committee and to the accredited METC that
544 approved the protocol, according to the requirements of that METC.

545 **8.2.1 Suspected unexpected serious adverse reactions (SUSAR)**

546 Adverse reactions are all untoward and unintended responses to an investigational product
547 related to any dose administered.

548

549 Unexpected adverse reactions are adverse reactions, of which the nature, or severity, is not
550 consistent with the applicable product information (e.g. Investigator's Brochure for an
551 unapproved IMP or Summary of Product Characteristics (SPC) for an authorised medicinal
552 product).

553

554 The Steering Committee will report expedited the following SUSARs through the web portal
555 *ToetsingOnline* to the METC:

556 – SUSARs that have arisen in the clinical trial that was assessed by the METC;

557 – SUSARs that have arisen in other clinical trials of the same sponsor and with the same
558 medicinal product, and that could have consequences for the safety of the subjects
559 involved in the clinical trial that was assessed by the METC.

560 The remaining SUSARs are recorded in an overview list (line-listing) that will be submitted
561 once every half year to the METC. This line-listing provides an overview of all SUSARs from
562 the study medicine, accompanied by a brief report highlighting the main points of concern.
563 The expedited reporting of SUSARs through the web portal *ToetsingOnline* is sufficient as
564 notification to the competent authority.

565

566 The Steering Committee will report expedited all SUSARs to the competent authorities in
567 other Member States, according to the requirements of the Member States.

568

569 The expedited reporting will occur not later than 15 days after the Steering Committee has
570 first knowledge of the adverse reactions. For fatal or life threatening cases the term will be
571 maximal 7 days for a preliminary report with another 8 days for completion of the report.

572

573 **8.2.2 Annual safety report**

574 In addition to the expedited reporting of SUSARs, the Steering Committee will submit, once a
575 year throughout the clinical trial, a safety report to the accredited METC, competent
576 authority, Medicine Evaluation Board and competent authorities of the concerned Member
577 States.

578 This safety report consists of:

- 579 – a list of all suspected (unexpected or expected) serious adverse reactions, along with an
580 aggregated summary table of all reported serious adverse reactions, ordered by organ
581 system, per study;
- 582 – a report concerning the safety of the subjects, consisting of a complete safety analysis
583 and an evaluation of the balance between the efficacy and the harmfulness of the
584 medicine under investigation.

585

586 **8.3 Follow-up of adverse events**

587 All adverse events will be followed until they have abated, or until a stable situation has
588 been reached. Depending on the event, follow up may require additional tests or medical
589 procedures as indicated, and/or referral to the general physician or a medical specialist. All
590 infants will participate in the usual NICU follow-up program. This program is targeted at
591 evaluating and coordinating diagnostic procedures and treatment of all prematurity related
592 problems, in close cooperation with regional and local pediatricians.

593

594 **8.4 Data Monitoring Committee (DMC)**

595 An external Data Monitoring Committee (DMC) will conduct reviews of patient safety
596 presented initially on hydrocortisone vs. placebo basis. Data summaries for the DMC will be
597 prepared by a statistician who is not a member of the investigating team. Formal interim
598 analyses will be conducted when approximately 25%, 50% and 75% of the anticipated
599 outcome data are available. The DMC will have access to all safety data and will be in a
600 position to make recommendations to the trial's Steering Committee - should a risk to the
601 safety of participants arise. This safety data will include, but not be restricted to, serious
602 adverse events and the safety outcomes listed as secondary outcomes. The results of the

603 interim analyses will remain confidential – only the unblinded statistician will have access to
604 the unblinded analyses. If the DMC recommends modification or cessation of the study
605 protocol, this will be discussed with the Steering Committee, who will make the decision.
606 The DMC will be composed of 5 individuals with expertise and extensive experience in
607 newborn ventilation, trial management or statistics. The Steering Committee will propose a
608 detailed mandate and review this with the DMC, from the outset. None of the members will
609 be from institutions represented in the study. The DMC will report to the Steering
610 Committee with whom the onus of early closure will ultimately reside. Both the DMC and
611 the Steering Committee will be informed on the implications of recent information on
612 premature stopping of trials.

613

614 **9. ETHICAL CONSIDERATIONS**

615 **9.1 Regulation statement**

616 The study will be conducted according to the principles of the Declaration of Helsinki⁵³ and
617 in accordance with the Medical Research Involving Human Subjects Act (WMO).

618

619 **9.2 Recruitment and informed consent**

620 Patients will be recruited and their parents will be informed and asked for consent by the
621 attending paediatricians. Informed written consent must be obtained from the parents prior to
622 randomisation for the study. The patient information letter and informed consent are provided
623 in section I of the study dossier. The right of a parent or patient to refuse participation without
624 giving reasons will be respected. The parents will remain free to withdraw their child at any
625 time from the study without consequences for further treatment.

626

627 **9.3 Benefits and risks assessment, group relatedness**

628 Burden: All infants participating in (either treatment arm of) the study are subjected to
629 routine neonatal intensive care. The administration of the study intervention itself
630 (hydrocortisone or placebo administration) does not pose an extra burden on the patients.
631 This study does not require extra investigations or interventions.

632 Benefit and risks: Hydrocortisone may facilitate extubation and thereby reduce the total
633 duration of mechanical ventilation. In addition, hydrocortisone may reduce the incidence of
634 BPD. Both these beneficial effects may improve neurodevelopmental outcome. On the other
635 hand, use of hydrocortisone may increase the risk for hyperglycemia, hypertension, systemic
636 infection, gastrointestinal perforation and a delay in neurodevelopment. However,
637 gastrointestinal perforation and delayed neurodevelopment have only been reported in
638 studies administering corticosteroids in the first week of life and/or in combination with
639 other medication. In this study the risk of gastrointestinal perforation and delayed
640 neurodevelopment may be reduced because hydrocortisone will be administered after the
641 first week of life and will not be combined with other drugs that are known to increase the
642 risk for these adverse effects. Infants assigned to the placebo group will not benefit from the
643 aforementioned possible beneficial effects nor be subjected to the possible adverse effect of
644 hydrocortisone.

645 Group relatedness: BPD is a complication occurring exclusively in preterm infants. Any
646 intervention aiming to reduce the risk of this complication therefore needs to be studied in
647 this specific population at risk.

648

649 **9.4 Compensation for injury**

650 The sponsor/investigator has a liability insurance which is in accordance with article 7,
651 subsection 6 of the WMO. The sponsor (also) has an insurance which is in accordance with

652 the legal requirements in the Netherlands (Article 7 WMO and the Measure regarding
653 Compulsory Insurance for Clinical Research in Humans of 23rd June 2003). This insurance
654 provides cover for damage to research subjects through injury or death caused by the study.
655 1. € 450.000,-- (i.e. four hundred and fifty thousand Euro) for death or injury for each
656 subject who participates in the Research;
657 2. € 3.500.000,-- (i.e. three million five hundred thousand Euro) for death or injury for all
658 subjects who participate in the Research;
659 3. € 5.000.000,-- (i.e. five million Euro) for the total damage incurred by the organization
660 for all damage disclosed by scientific research for the Sponsor as ‘verrichter’ in the
661 meaning of said Act in each year of insurance coverage.
662 The insurance applies to the damage that becomes apparent during the study or within 4 years
663 after the end of the study.

664

665 **9.5 Incentives**

666 Participants will not receive a financial compensation for participation as an incentive.

667

668 **10. ADMINISTRATIVE ASPECTS AND PUBLICATION**

669 **10.1 Handling and storage of data and documents**

670 Datamanagement will be implemented according to Good Clinical Practice (GCP)-guidelines.

671 Patient data will be entered by way of an eCRF in a central GCP proof internet based

672 database to facilitate on-site data-entry. Security is guaranteed with login names, login

673 codes and encrypted data transfer. An experienced datamanager will maintain the database

674 and check the information in the database for completeness, consistency and plausibility.

675

676 The data of all subjects will be coded and this coding will not be retraceable to the individual
677 patient. The key to this coding is safeguarded by the investigator. A limited number of
678 people have access to the source data. These are the principal investigator, investigating
679 doctor and investigating personnel. Personal data are only processed by the researchers or
680 by those who fall directly under their authority. In addition, the study monitor, quality
681 assurance auditor, employees from the METC and the Health Care Inspectorate of the
682 Ministry of Health, welfare and Sport (Nederlandse Inspectie voor de Gezondheidszorg) have
683 access to the source data. All are subject to the pledge of confidentiality. Data and human
684 material will be stored for 15 years strictly confidential.

685

686 **10.2 Amendments**

687 Amendments are changes made to the trial after a favourable opinion by the accredited METC
688 has been given. All amendments will be notified to the METC that gave a favourable opinion.
689 All substantial amendments will be notified to the METC and to the competent authority.
690 Non-substantial amendments will not be notified to the accredited METC and the competent
691 authority, but will be recorded and filed by the Steering Committee.

692

693 **10.3 Annual progress report**

694 If requested, an annual progress report of the progress of the trial will be provided to the
695 accredited METC. Information will be provided on the date of inclusion of the first subject,
696 numbers of subjects included and numbers of subjects that have completed the trial, serious
697 adverse events/ serious adverse reactions, other problems, and amendments. In case the study
698 is ended prematurely, the investigator will notify the accredited METC, including the reasons
699 for the premature termination. Within one year after the end of the study, the

700 investigator/sponsor will submit a final study report with the results of the study, including
701 any publications/abstracts of the study, to the accredited METC.

702

703 **10.4 Public disclosure and publication policy**

704 The study will be registered in the EUDRACT, the website of the Dutch National Competent
705 Authority, the 'Centrale Commissie Mensgebonden Onderzoek' (CCMO), Dutch public trial
706 registry, part of the WHO registry. The results of the study will be published in peer-
707 reviewed international medical journals. In addition, the results of the study will be used for
708 development and implementation of a guideline on treatment of BPD, which will benefit
709 future patients.

710

711 **11. Organisation**

712 Steering Committee

713 The Steering Committee is the main policy and decision making committee of the study and
714 has final responsibility for the scientific conduct of the study. It will be composed of
715 representatives of the sponsors, of the investigators of the participating centres and of the
716 MCRN. The specific tasks of the Steering Committee are:

- 717 • Approve the study protocol
- 718 • Approve necessary changes in the protocol based on considerations of feasibility
- 719 • Act upon recommendations of the Data Monitoring Committee
- 720 • Review performance reports of the study sites
- 721 • Resolve operational problems brought before it by the project manager
- 722 • Approve study reports and papers for publication.

723

724 Data Monitoring Committee

725 An independent Data Monitoring Committee (DMC) will be created specifically for this trial.

726 The DMC will act in advisory capacity to the Steering Committee . See Paragraph 8.4 for a

727 description of the membership, tasks and responsibilities of the DMC.

728

729 Clinical Project Manager / Central Study Coordinator

730 An experienced clinical project manager (CPM) from MCRN will manage the quality of the

731 study according to the Good Clinical Practice (GCP)-guidelines, supervise the data monitoring

732 process, and verify the quality of conduct of all study personnel. The CPM and/or clinical

733 research associate (CRA) will arrange that the study personnel is adequately trained in GCP

734 and study protocol, where needed. The CPM meets regularly with the CRA, data managers,

735 the Data Safety Monitoring Committee (DSMC), financial departments of study centers, and

736 all other relevant parties to assure study progress, quality and financials are according to

737 planning. The CPM will coordinate regulatory authority and ethics committee submissions.

738 The CPM provides regularly an overall study status report to the Steering Committee

739

740 Study Monitoring

741 The study will be monitored by an experienced monitor from MCRN throughout its duration

742 by means of personal visits to the Investigator's facilities and through other communications

743 (e.g., telephone calls, written correspondence).

744 Monitoring visits will be scheduled at mutually agreeable times periodically throughout the

745 study and at frequency deemed appropriate for the study.

746 These visits will be conducted to evaluate the progress of the study, ensure the rights and

747 wellbeing of the subjects are protected, check that the reported clinical study data are

748 accurate, complete and verifiable from source documents, and the conduct of the study is in

749 compliance with the approved protocol and amendments, GCP and applicable national
750 regulatory requirements. A monitoring visit will include a review of the essential clinical
751 study documents (regulatory documents, CRFs, source documents, drug disposition records,
752 subject informed consent forms, etc.) as well as discussion on the conduct of the study with
753 the Investigator and staff. The Investigator and staff should be available during these visits to
754 facilitate the review of the clinical study records and resolve/document any discrepancies
755 found during the visit.

756

757 Quality Assurance Audits and Inspections

758 The Sponsor's (or an authorized representative's) Quality Assurance department may conduct
759 audits of all aspects of the clinical study either during the study or after the study has been
760 completed. By participating this trial the investigator agree to this requirement.

761 The clinical study may also be subject to inspection by regulatory authorities as well as the
762 accredited Medical Ethical Committee/ Competent authority to ascertain that the study is
763 being or has been conducted in accordance with protocol requirements, GCP, as well as the
764 applicable regulatory requirements.

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930 APPENDIX 1

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Afdeling Neonatologie

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STUDIE MEDICATIE SCHEMA

940

941 voor: [Klik hier en typ naam]

942 geboren op: [Klik hier en typ geboortedatum]

943

Gewicht: kg.startdatum:

| | Frequentie | mg/dosis | | Frequentie | mg/dosis |
|-----------|------------|----------|-----------|------------|----------|
| 1-jan-11 | 4 x | 0 mg. | 13-jan-11 | 2 x | 0 mg. |
| 2-jan-11 | 4 x | 0 mg. | 14-jan-11 | 2 x | 0 mg. |
| 3-jan-11 | 4 x | 0 mg. | 15-jan-11 | 2 x | 0 mg. |
| 4-jan-11 | 4 x | 0 mg. | 16-jan-11 | 2 x | 0 mg. |
| 5-jan-11 | 4 x | 0 mg. | 17-jan-11 | 2 x | 0 mg. |
| 6-jan-11 | 4 x | 0 mg. | 18-jan-11 | 1 x | 0 mg. |
| 7-jan-11 | 4 x | 0 mg. | 19-jan-11 | 1 x | 0 mg. |
| 8-jan-11 | 3 x | 0 mg. | 20-jan-11 | 1 x | 0 mg. |
| 9-jan-11 | 3 x | 0 mg. | 21-jan-11 | 1 x | 0 mg. |
| 10-jan-11 | 3 x | 0 mg. | 22-jan-11 | 1 x | 0 mg. |
| 11-jan-11 | 3 x | 0 mg. | | | |
| 12-jan-11 | 3 x | 0 mg. | | | |

944

945

946 Opmerkingen: [Klik hier en typ opmerkingen]

947

948 Naam arts: [Klik hier en typ naam arts]

949 sein: [Klik hier en typ seinnummer]

950

951 Paraaf:

952

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956 **APPENDIX 2**

957

958 **Oxygen reduction test**

959 Bronchopulmonary dysplasia (BPD) can be classified in to mild, moderate or severe
960 depending on the amount and duration of supplemental oxygen and the level of respiratory
961 support. If a patient has received supplemental oxygen for more than 28 d ($FiO_2 > 0.21$ for
962 more than 12 hours each day) and is receiving no extra oxygen at 36 weeks postmenstrual
963 age (PMA), he or she is classified as having mild BPD. If the oxygen need at 36 weeks PMA is
964 between 0.21 and 0.30, BPD is classified as moderate and in case of a $FiO_2 > 0.30$ and/or
965 receiving continuous positive airway pressure (nCPAP)/mechanical ventilation as severe.
966 It is important to realize that the duration of supplemental oxygen is highly dependent on
967 target ranges of transcutaneous oxygen saturation (SpO_2) and the alertness of the clinician
968 to actively wean oxygen delivery.

969 To make sure that patients receive supplemental oxygen for pulmonary reasons and to
970 standardize the amount of oxygen to predefined and uniform SpO_2 targets, Walsh et al.
971 developed a so-called oxygen reduction test at 36 weeks PMA. Patients are eligible for
972 testing if they need a FiO_2 between 0.21 and 0.30 to maintain the SpO_2 between 90-96% **or** if
973 they receive a $FiO_2 > 0.30$ resulting in a $SpO_2 > 96\%$. Patients supported with nasal cannulae
974 (flow not nCPAP) without supplemental oxygen, and patients treated with
975 nCPAP/mechanical ventilation or with a $FiO_2 > 0.30$ resulting in a $SpO_2 < 96\%$ do not need
976 additional testing, and are, respectively, classified as having mild and severe BPD.

977 ***The oxygen reduction test***978 **Indications:**

979 - $\text{FiO}_2 > 0.21$ and < 0.30 with oxygen saturation ranges between 90% and 96%

980 - $\text{FiO}_2 > 0.30$ with a oxygen saturation range above 96%

981 Methods:

982 The patient is placed in supine position and the test is initiated 30 minutes after a feeding. The
983 supplemental oxygen requirement will be gradually weaned to room air while monitoring
984 SpO_2 . The diagnosis moderate BPD can be rejected when the SpO_2 remain above $\geq 88\%$ in
985 room air during 1 hour without apnea or bradycardia.

986 The diagnosis moderate BPD is confirmed if the saturation goes below 80% during > 1 minute
987 or remains between 80-87% during > 5 minutes. All occurrences of movement artifact
988 (defined as visible motion of the infant together with loss of plethysmograph signal from the
989 monitor) are recorded and corresponding saturation values are to be deleted.

990

991 The test contains 4 phases

992 Phase 1: Baseline evaluation

993 For 15 minutes heart rate, respiratory rate, SpO_2 , number of apnea (cessation of breathing $>$
994 20 seconds) and bradycardia (heart rate $< 80/\text{min}$ during > 10 sec) will be collected.

995 Phase 2: Oxygen reduction

996 The supplemental oxygen will be weaned by 2% to room air, after which the flow will be
997 weaned with 0.1 L/min to 0 L/min; The nasal cannulae will be removed from the nares, but
998 not removed from the face.

999 Phase 3: Observation period

1000 For the period of 1 hour the heart rate, respiratory rate, and SpO_2 in room air will be
1001 registered. In case of a desaturation below 80% for > 1 minute or saturation between 80-87%
1002 for > 5 minutes, the supplemental oxygen will be restarted and the test will be aborted.

1003 *Phase 4: Back to situation before the test*

1004 The level of supplemental oxygen and flow will be reset to the status before the test.

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1053 PROTOCOL

1054 **Systemic Hydrocortisone To Prevent Bronchopulmonary Dysplasia in preterm**1055 **infants: the SToP-BPD study**1056 **A multicenter randomised placebo controlled trial**

| | |
|-------------------------------|---|
| Protocol ID | Systemic Hydrocortisone To Prevent Bronchopulmonary Dysplasia in preterm infants: the SToP-BPD study |
| Short title | SToP-BPD Study |
| Version | 2 |
| Date | 05 January 2011 |
| Principal investigator | Anton van Kaam Department of Neonatology (Room H3-228) Emma Children's Hospital AMC PO Box 22700, 1100 DD, Amsterdam, The Netherlands Tel: +31-20-5663971, Fax: +31-20-6965099 Email: a.h.vankaam@amc.uva.nl |
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1077 SUMMARY

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1122 **LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS**

1123

| | | |
|------|---------|--|
| 1124 | ARR | Absolute Risk Reduction |
| 1125 | BPD | BronchoPulmonary Dysplasia |
| 1126 | BW | Birth Weight |
| 1127 | CDP | Continuous Distension Pressure |
| 1128 | CGA | Corrected Gestational Age |
| 1129 | CP | Cerebral Palsy |
| 1130 | DNRN | Dutch Neonatal Research Netwerk; in Dutch: Nederlands Neonataal |
| 1131 | | Research Netwerk (NNRN) |
| 1132 | DSMB | Data Safety Monitoring Board |
| 1133 | ESEMC | External Safety and Efficacy Monitoring Committee |
| 1134 | GA | Gestational Age |
| 1135 | HFO | High Frequency Oscillation |
| 1136 | IMP | Investigational Medicinal Product |
| 1137 | IVH | IntraVentricular Haemorrhage |
| 1138 | MAwP | Mean Airway Pressure |
| 1139 | METC | Medical research ethics committee (MREC); in Dutch: Medisch |
| 1140 | | Ethische Toetsing Commissie |
| 1141 | MRI | Magnetic Resonance Imaging |
| 1142 | NEC | Necrotising EnteroColitis |
| 1143 | NICU | Neonatal Intensive Care Unit |
| 1144 | NICHD | National Institutes for Child Health and Human Development |
| 1145 | NNT | Number Needed to Treat |
| 1146 | NVK | Dutch Society of Pediatricians; in Dutch: Nederlandse Vereniging voor |
| 1147 | | Kindergeneeskunde |
| 1148 | PDA | Persistent Ductus Arteriosus |
| 1149 | PMA | PostMenstrual Age |
| 1150 | PNA | PostNatal Age |
| 1151 | PVL | PeriVentricular Leucomalacia |
| 1152 | RCT | Randomised Controlled Trial |
| 1153 | RI | Respiratory Index |
| 1154 | SAE | Serious Adverse Event |
| 1155 | SD | Standard Deviation |
| 1156 | Sponsor | The sponsor is the party that commissions the organisation of |
| 1157 | | performance of the research, for example a pharmaceutical company, |
| 1158 | | academic hospital, scientific organisation or investigator. A party that |
| 1159 | | provides funding for a study but does not commission it is not |
| 1160 | | regarded as the sponsor, but referred to as a subsidising party. |
| 1161 | VLBW | Very Low Birth Weight |
| 1162 | WMO | Medical Research Involving Human Subjects Act; in Dutch: Wet |
| 1163 | | Medisch-wetenschappelijk Onderzoek met Mensen |
| 1164 | | |

1165

1166 **SUMMARY**

1167 **Background:** Randomised controlled trials (RCTs) have shown that treatment of chronically
1168 ventilated preterm infants after the first week of life with dexamethasone reduces the
1169 incidence of bronchopulmonary dysplasia (BPD). However, there are concerns that its use
1170 may increase the risk of adverse neurodevelopmental outcome. Hydrocortisone has been
1171 suggested as an alternative therapy. So far no RCT has investigated its efficacy when
1172 administered after the first week of life to ventilated preterm infants.

1173 **Objective:** To establish the efficacy of hydrocortisone given after one week of life to reduce
1174 the incidence of the combined outcome death or BPD in chronically ventilated preterm
1175 infants.

1176 **Study design:** Randomised double blind placebo controlled multicenter study.

1177 **Study population:** Very low birth weight infants (GA<30weeks and/or BW<1250grams),
1178 ventilator dependent at a postnatal age of 7 – 14 days.

1179 **Intervention:** Administration of hydrocortisone or placebo during a 22 day tapering
1180 schedule.

1181 **Outcome parameters:** Primary outcome measure is survival free of BPD at 36 weeks
1182 postmenstrual age (PMA). Secondary outcomes are short term effects on the pulmonary
1183 condition, adverse effects during hospitalization, and long-term neurodevelopmental
1184 sequelae assessed at 2 years corrected gestational age (CGA).

1185 **Burden, benefit and risks associated with participation; group relatedness:**

1186 Burden: All infants participating in (either treatment arm of) the study are subjected to
1187 routine neonatal intensive care. The administration of the study intervention itself
1188 (hydrocortisone or placebo administration) does not pose an extra burden on the patients.
1189 This study does not require extra investigations or interventions.

1190 Benefit and risks: Hydrocortisone may facilitate extubation and thereby reduce the total
1191 duration of mechanical ventilation. In addition, hydrocortisone may reduce the incidence of
1192 BPD. Both these beneficial effects may improve neurodevelopmental outcome. On the other
1193 hand, use of hydrocortisone may increase the risk for hyperglycemia, hypertension, systemic
1194 infection, gastrointestinal perforation and a delay in neurodevelopment. However,
1195 gastrointestinal perforation and delayed neurodevelopment have only been reported in
1196 studies administering corticosteroids in the first week of life and/or in combination with
1197 other medication. In this study the risk of gastrointestinal perforation and delayed
1198 neurodevelopment may be reduced because hydrocortisone will be administered after the
1199 first week of life and will not be combined with other drugs that are known to increase the
1200 risk for these adverse effects. Infants assigned to the placebo group will not benefit from the
1201 aforementioned possible beneficial effects nor be subjected to the possible adverse effect of
1202 hydrocortisone.

1203 Group relatedness: BPD is a complication occurring exclusively in preterm infants. Any
1204 intervention aiming to reduce the risk of this complication therefore needs to be studied in
1205 this specific population at risk.

1206 **1. BACKGROUND**

1207 Bronchopulmonary dysplasia (BPD) is the most common complication of premature birth,
1208 with a reported incidence of 8% to 35%.^{1,2} BPD is characterized by chronic respiratory
1209 distress, the need for prolonged respiratory support, an increased risk of recurrent
1210 pulmonary infections, airway hyperreactivity during the first years of life³ and life-long
1211 alterations in lung function.⁴⁻⁶ Patients with established BPD have high rates of readmissions
1212 and utilization of health services resulting in tremendous societal costs compared to children
1213 without BPD.⁷⁻⁹ Furthermore, BPD is considered an important risk factor for adverse
1214 neurodevelopmental outcome after premature birth¹⁰⁻¹⁴ with life-long economic and social
1215 consequences.¹⁵⁻¹⁸

1216

1217 In addition to direct mechanical injury, caused by artificial ventilation and oxygen toxicity,
1218 pulmonary inflammation has been identified as an important mediator in the development
1219 of BPD.¹⁹⁻²¹ This is the rationale for treating patients with glucocorticoids, a well known anti-
1220 inflammatory agent. Randomised controlled trials (RCTs) summarized in several systematic
1221 reviews have shown that postnatal systemic glucocorticoids, mainly dexamethasone, reduce
1222 the risk of the combined outcome death or BPD in ventilated preterm infants.²²⁻²⁴

1223 Furthermore, systemic glucocorticoids seem to be most effective when administered in a
1224 time frame of 7 to 14 days postnatal age, the so-called moderately early treatment
1225 onset.^{25,26} However, initiating dexamethasone treatment in the first days of life seems to be
1226 associated with an increased the risk of cerebral palsy (CP). Although this complication has
1227 not been reported by RCTs investigating dexamethasone treatment initiated after the first
1228 week of life, these alarming reports have resulted in a general concern on the use of
1229 dexamethasone in preterm infants.²⁷⁻²⁹ Based on this concern, the American Academy of

1230 Pediatrics, Canadian Paediatric Society, and the European Association of Perinatal Medicine
1231 have stated that clinical trials should be performed to investigate the use of alternative anti-
1232 inflammatory glucocorticoids, such as the less potent glucocorticoid hydrocortisone.^{30,31}
1233
1234 Despite the ongoing concerns on their use, systemic glucocorticoids are still used in
1235 approximately 10% of the preterm infants at risk for BPD.³²⁻³⁴ Dexamethasone is still the
1236 most widely used glucocorticoid drug, but its dose has been significantly reduced and
1237 administration is often postponed until the 3rd or 4th week of life.²⁷
1238
1239 As an alternative, many clinicians have started to use hydrocortisone. Animal data suggest
1240 that hydrocortisone has a less detrimental effect on the brain than dexamethasone.³⁵
1241 However, no placebo controlled RCT has investigated the use of hydrocortisone after the
1242 first week in life in ventilator dependent preterm infants.³⁶ Six RCTs investigating a low
1243 hydrocortisone dose started within < 72 hours after birth (early treatment) failed to show a
1244 clear reduction in the incidence of BPD.³⁷⁻⁴² Only one of these trials reported long-term
1245 follow-up, showing no differences in adverse neurodevelopmental sequelae.⁴³ These
1246 findings are supported by several historical cohort studies, showing no increased risk of
1247 adverse neurodevelopmental outcome in hydrocortisone treated infants.⁴⁴⁻⁴⁶
1248
1249 In most Dutch Neonatal Intensive Care Units (NICUs) preterm infants who are ventilator-
1250 dependent in the second week of life are no longer treated with glucocorticoids. Infants are
1251 kept on the ventilator allowing spontaneous recovery of lung function over time, sometimes
1252 supported by other interventions, such as diuretics and inhalation therapy. With this
1253 approach, some infants can be successfully weaned and extubated. Only those infants that

1254 remain ventilator dependent after 3-4 weeks are treated with glucocorticoids, with the
1255 primary objective to wean and extubate.

1256 Although this approach will undoubtedly result in successful extubation of most infants with
1257 the lowest possible use of glucocorticoids, the questions remains if this is also the best
1258 strategy in reducing the incidence of BPD in preterm infants ventilated after 7 days of life.
1259 This questions seems justified and relevant because BPD, and not failure to extubate, is
1260 associated with adverse medium- and long-term outcome. This is the main reason why the
1261 primary outcome of this study is death or BPD and not failure to extubate.

1262

1263 The NICU at the University Medical Center Utrecht, has historically used hydrocortisone for
1264 chronically ventilated preterm infants. Retrospective studies seem to indicate that
1265 hydrocortisone is effective in reducing BPD, without causing serious adverse effects.
1266 However, these findings need to be confirmed or refuted by a large randomized placebo
1267 controlled trial. Despite the absence of randomized evidence, three out of the 10 Dutch
1268 NICUs switched from dexamethasone to hydrocortisone. This diversity in treatment between
1269 NICUs is undesirable and has also been debated in the public press.⁴⁷ As a first step to
1270 resolve this diversity in treatment, all 10 Dutch NICUs have indicated that a RCT comparing
1271 hydrocortisone with placebo is urgently needed, an initiative that is also supported by the
1272 Dutch Society of Pediatricians (NVK), giving such a trial top priority. Since the NICUs which
1273 already use hydrocortisone are reluctant or refuse to prescribe dexamethasone as trial
1274 medication, a RCT comparing dexamethasone versus hydrocortisone is not possible.

1275

1276 The optimal dose of hydrocortisone is currently unknown. However, the NICU in Utrecht has
1277 been using a fixed hydrocortisone treatment regimen for several decades now and this

1278 regimen has also been adopted by the other Dutch NICUs using hydrocortisone.
1279 Retrospective studies strongly suggest that this is a safe dose, because it was not associated
1280 with an increased risk of adverse neurological outcome.^{45,48} Comparing hydrocortisone
1281 treated patients with dexamethasone treated patients in other NICUs showed no difference
1282 in the incidence of BPD, suggesting that this dose is equally effective in reducing BPD.⁴⁸
1283 Based on these findings and current clinical practice, we decided to adopt the dosing
1284 regimen from Utrecht for this study.

1285

1286 *Based on the current available evidence, the American Academy of Pediatrics has concluded*
1287 *that: (1) routine use of systemic dexamethasone for the prevention or treatment of CLD in*
1288 *infants with VLBW is not recommended; (2) outside the context of a randomized, controlled*
1289 *trial, the use of corticosteroids should be limited to exceptional clinical circumstances. Based*
1290 *on these recommendation ventilated preterm infants are no longer routinely treated with*
1291 *postnatal corticosteroids. Furthermore, in exceptional cases treatment is postponed until*
1292 *after the third week of life. Comparison of hydrocortisone to a placebo is therefore warranted*
1293 *because standard therapy in the second week of life (7-14 d after birth) is to wait for*
1294 *spontaneous recovery of lung function. In exceptional clinical circumstances treatment with a*
1295 *(rescue) open label glucocorticoids is still possible in the current study.*

1296 Although based on the above, the *extra* risks for the patients in this study are probably
1297 limited, a data monitoring committee will closely monitor any possible adverse effects and
1298 risks, as also explained in paragraph 8.4.

1299

1300 **2. OBJECTIVE**

1301 To investigate if hydrocortisone is safe and effective in reducing the incidence of the
1302 combined outcome death or BPD at 36 weeks PMA in chronically ventilated preterm infants,
1303 as compared to placebo. This study **does not** aim to successfully extubate ventilator-
1304 dependent preterm infants with the lowest possible use of glucocorticoids (i.e.
1305 hydrocortisone), but to use glucocorticoids as an early intervention (7-14 d after birth) to
1306 reduce the risk of death or BPD in these ventilator-dependent preterm infants. From this
1307 point of view the treatment strategy is fundamentally different from what is currently used
1308 in daily clinical practice.

1309

1310 **3. STUDY DESIGN**

1311 Multicenter randomised double-blind placebo-controlled trial.

1312

1313 **4. STUDY POPULATION**

1314 **4.1 Population eligibility**

1315 Ventilated VLBW infants at high risk for BPD treated in a level III NICU

1316

1317 **4.2 Inclusion criteria**

1318 Preterm infants with:

- 1319 - a gestational age < 30 wks and/or birth weight < 1250 g
- 1320 - ventilator dependent at 7-14 days PNA
- 1321 - a respiratory index (MAwP x FiO₂) of ≥ 3.5 for more than 12 h/day for at least 48
1322 hours, ensuring normal oxygen saturation (86-94%) and pCO₂ values in premature
1323 infants (5.0-7.0 kPa).

1324

1325 **4.3 Exclusion criteria**

- 1326 - chromosomal defects (e.g. trisomy 13, 18, 21)
- 1327 - major congenital malformations that:
- 1328 ○ compromise lung function (e.g. surfactant protein deficiencies, congenital
 - 1329 diaphragmatic hernia)
 - 1330 ○ result in chronic ventilation (e.g. Pierre Robin sequence)
 - 1331 ○ increase the risk of death or adverse neurodevelopmental outcome
 - 1332 (congenital cerebral malformations)
- 1333 - Use of dexamethasone or hydrocortisone for the sole purpose of improving lung
- 1334 function and respiratory status

1335

1336 Although (suspected or proven) sepsis, pneumonia, necrotizing enterocolitis (NEC) and

1337 patent ductus arteriosus (PDA) are well-known causes of respiratory failure, these diagnoses

1338 are known to be independent risk factors for developing BPD. Therefore, these diagnoses are

1339 not considered to be exclusion criteria. The following should be taken into consideration:

1340 4. In ventilator-dependent cases of sepsis and pneumonia the attending physician may

1341 start antibiotics and await the effect on respiratory drive/ pulmonary status for 48

1342 hours. If the patient meets the inclusion criteria after 48 h, he/she is eligible for

1343 inclusion.

1344 5. It is strongly recommended to screen all ventilator-dependent preterm infants for a

1345 PDA at 5 days PNA. In case of a hemodynamically important PDA, medical intervention

1346 according to local protocols should be started as soon as possible. Ibuprofen or

1347 indomethacin treatment should not be combined with glucocorticoids, because it has

1348 been suggested that this combination will increase the risk of intestinal perforation.

1349 If, subsequently, the patient can't be extubated following medical treatment or

1350 requires surgical PDA closure, he/she should be included in the study - provided that
1351 all inclusion criteria are met.

1352 6. If the physician considers extubation not an option because of the general condition
1353 of the infant (e.g. NEC with severe hemodynamic instability and severe abdominal
1354 distension) inclusion in the study can be postponed until the maximum of 14 days
1355 PNA.

1356 **4.4 Sample size calculation**

1357 The primary outcome parameter is BPD free survival at 36 weeks PMA. The a priori risk of
1358 death or BPD in preterm infants less than 30 weeks gestation and ventilated in the second
1359 week of life is estimated at 60 – 70%. The meta-analysis on moderately early
1360 dexamethasone treatment estimated an absolute risk reduction (ARR) of 25% (NNT=4)
1361 compared with placebo.²⁴ However, there are no data currently available on the efficacy of
1362 hydrocortisone and the suggested cumulative dose in the present study is considerably
1363 lower compared to previously used dexamethasone doses. Since the shown efficacy of
1364 dexamethasone is dependent on the used doses in these trials²⁶, we would propose a more
1365 conservative approach, defining an ARR of 15% or more (NNT=7) as clinically relevant. With
1366 an estimated *a priori* risk for death or BPD at 36 weeks PMA of 60%, a type I error of 5% (2
1367 tailed) and a power of 80% the number of patients to be included in each treatment arm
1368 would be 175 (total 350). Anticipating a 10% drop out of randomized patients, 200 patients
1369 need to be included in each treatment arm (total 400). Based on a retrospective analysis of
1370 ventilated preterm infants at day 7 of life in the majority of Dutch NICUs we expect a total of
1371 200 eligible patients each year. With an estimated inclusion rate of 66% of eligible patients
1372 and an inclusion period of 3 years, a total of 400 patients should be included in the study.
1373 For sample size calculation we used Nquery (Statistical Solutions Ltd., Cork, Ireland).

1374

1375 **5. METHODS**1376 **5.1 Randomisation, blinding and treatment allocation**

1377 Written informed consent has to be obtained from either parents or care-givers prior to
1378 randomisation. In case of ventilator dependency after day 7 of life with a suspected diagnosis
1379 of developing BPD, parents receive the study information as soon as possible allowing them
1380 sufficient time to consider participation. The actual decision to include the patient in the trial
1381 should be made between day 7 and 14 PNA. The first dose of study medication should be
1382 administered within 72 hours after this decision. Randomization will be centrally controlled
1383 and web-based using a computer program designed for this study. This trial will be protected
1384 from selection bias by using concealed, stratified and blocked randomisation.

1385

1386 Randomisation will be stratified per center and according to gestational age stratum (Stratum
1387 A: 24-26 weeks; Stratum B: 26-28 weeks; Stratum C: >28 weeks), in order to achieve an
1388 equal distribution in both treatment arms. The allocation ratio will be 1:1 with block
1389 randomisation using variable block sizes. Multiple birth infants will be randomised
1390 independently, unless the parents or caretakers explicitly demand that the siblings should be
1391 treated according to the same treatment arm. An automated mechanism to perform twin
1392 randomisation is in place.

1393 The infants' parents and all members of the medical team, including investigators, remain
1394 blinded to group assignment throughout the study.

1395

1396 Patient characteristics, including gestational age, birth weight and respiratory status, will be
1397 collected from all eligible infants that are not included in the study. In addition, we will

1398 collect data on why the patients were not included. With this information we will assess
1399 possible bias in patient inclusion.

1400

1401 **5.2 Withdrawal of individual subjects**

1402 Parents or caregivers can leave the study at any time for any reason if they wish to do so
1403 without any consequences. The investigator/attending physician can decide to withdraw a
1404 subject from the study in case of prespecified treatment failure (see section 6.1.2).

1405

1406 **5.3 Replacement of individual subjects after withdrawal**

1407 The number of withdrawn patients not marked as prespecified treatment failure (see section
1408 6.1.2) will be replaced.

1409

1410 **5.4 Follow-up of subjects withdrawn from treatment**

1411 Subjects withdrawn from the study will be treated according to the standard of care, including
1412 neurodevelopmental outcome assessment at the outpatient clinic.

1413

1414 **5.5 Premature termination of the trial**

1415 An independent *Data Safety Monitoring Board* will monitor the study on safety aspects (see
1416 section 8.4) and if necessary recommend termination of the study.

1417

1418 **6. TREATMENT OF SUBJECTS**

1419 **6.1. Therapeutic details**

1420 6.1.1 Preparation of the trial medication: Both hydrocortisone and placebo will be prepared
1421 according to GMP guidelines. In close collaboration with the AMC pharmacy (Dr. M.
1422 Kemper) we are currently investigating the best way of preparing and supplying the drugs to

1423 the participating centers. We will provide this information at a later date. The infants of the
1424 hydrocortisone group will receive hemisuccinate hydrocortisone 5mg/kg/day Q.I.D for 7
1425 days, followed by 3.75 mg/kg/day T.I.D. for 5 days, subsequently lowering the frequency by
1426 one dose every 5 day. This leads to a total duration of therapy of 22 days and a cumulative
1427 dose of 72.5 mg/kg hydrocortisone (see appendix 1). The infants in the control group receive
1428 saline placebo for the entire 22-day period in the same frequency as the hydrocortisone group.
1429 Both saline and hydrocortisone schedules will be calculated according to weight on the day of
1430 randomisation and not adjusted to the actual weight during the tapering schedule.

1431

1432 6.1.2 Stop criteria during study protocol medication (treatment failure): In case of life
1433 threatening deterioration of the pulmonary condition, the attending physician may decide to
1434 start open label corticosteroids therapy in an attempt to improve the pulmonary condition. At
1435 that point in time the study medication is stopped and the patient will be recorded as
1436 “treatment failure”. In case of treatment failure the following data will be collected: timing of
1437 treatment failure, ventilatory support and settings, type of open label medication, starting date,
1438 cumulative dose and duration of rescue therapy. The patients will be followed as all other
1439 patients until the clinical endpoints occur or until end of follow up.

1440

1441 6.1.3 Late rescue therapy outside study protocol (late rescue glucocorticoids): Patients still on
1442 mechanical ventilation after completion of the study medication, i.e. day 22, may be treated
1443 with open label corticosteroids. Data on type of open label medication, the starting date,
1444 cumulative dose and duration of rescue therapy are collected.

1445

1446 6.1.4 Anti-hypotensive therapy: In case of persistent hypotension, not (sufficiently)
1447 responding to first line treatment with intravascular volume expansion and inotropes

1448 (dopamine and/or dobutamine) the use of hydrocortisone. Treatment for hypotension will not
1449 be considered as treatment failure. Data on timing, dose and duration will be collected.

1450

1451 **6.2. Use of co-intervention**

1452 All randomized patients will be treated according to the guidelines of the individual NICUs.

1453 All participating NICUs explore treatable causes of ventilator dependency during the first
1454 week of life, such as patent ductus arteriosus, sepsis and pneumonia as much as possible and
1455 to treat these according to the department protocol. Although all of these conditions can be an
1456 alternative cause of respiratory failure, they are known risk factors for developing BPD and
1457 therefore are not considered exclusion criteria.

1458

1459 This trial will monitor the prognostically important co-interventions and conditions, as
1460 described in section 7.2.

1461

1462 **6.3. Endpoints**

1463 6.3.1. Primary endpoint: the dichotomous variable *BPD free survival at 36 weeks PMA*. BPD
1464 at 36 weeks PMA will be assessed according to the NIHCHD Consensus Statement defining
1465 normal oxygen saturation as 86%-94%. The severity of the BPD will be assessed as proposed
1466 by Jobe et.al.²¹, since the severity of BPD has a high association with neurodevelopmental
1467 sequelae.¹² In case of supplemental oxygen delivery >21% and < 30% or low flow at 36 weeks
1468 PMA, the oxygen reduction test as described by Walsh et.al.^{21,49,50} should be preformed. A
1469 positive oxygen reduction test has a high correlation with the risk on discharge home with
1470 oxygen, the length of hospital stay, and pulmonary morbidity requiring hospital readmission
1471 during the first year of life. For practical guidance on the use of the oxygen reduction test
1472 please go to appendix 2.

1473

1474 6.3.2. Secondary endpoints:

- 1475 • treatment failure as defined in section 6.1.2
- 1476 • mortality at 28 days PNA, 36 weeks PMA and at hospital discharge
- 1477 • BPD at 28 days
- 1478 • failure to extubate 3, 7, 14 and 21 days after initiating therapy
- 1479 • duration of mechanical ventilation
- 1480 • use of “rescue treatment” with hydrocortisone outside the study protocol
- 1481 • total time on supplemental oxygen
- 1482 • length of hospital stay
- 1483 • incidence of hypertension, defined as systolic blood pressure > 2SD of standardized
- 1484 values used in the department
- 1485 • hyperglycemia requiring the use of insulin therapy
- 1486 • nosocomial infection, like sepsis, meningitis and pneumonia
- 1487 • hemodynamic significant patent ductus arteriosus for which medical intervention or
- 1488 surgical ligation is needed
- 1489 • necrotising enterocolitis (NEC), diagnosed at surgery, autopsy or by radiographic
- 1490 finding of pneumatosis intestinalis or hepatobiliary gas (Bell stage II)
- 1491 • gastrointestinal bleeding
- 1492 • isolated gastrointestinal perforation diagnosed on abdominal radiography
- 1493 • intraventricular haemorrhage (IVH) and/or periventricular leucomalacia (PVL),
- 1494 including grading on cerebral ultrasonography according to protocol defined by Ment
- 1495 et.al.⁵¹
- 1496 • retinopathy of prematurity, including grading following international classification⁵²

- 1497 • weight gain, head circumference and length gain at 36 weeks PMA
- 1498 • long-term health and neurodevelopmental sequelae, assessed at 2 years CGA:
- 1499 ○ readmissions since first discharge home
- 1500 ○ weight, length and head circumference at 24 months c.a.
- 1501 ○ Bayley Scales of Infant Development III, Mental Developmental Index and
- 1502 Psychomotor Developmental Index
- 1503 ○ cerebral palsy and severity of cerebral palsy using gross motor function
- 1504 classification system
- 1505 ○ hearing loss requiring hearing aids
- 1506 ○ blindness
- 1507 ○ behavioural problems (child behaviour checklist)

1508

1509 All primary and secondary endpoints are measured as part of standard usual care in the
1510 Netherlands and will be derived from the charts of the patients by the investigators.

1511

1512 **7. DATA COLLECTION AND STATISTICAL ANALYSIS**

1513 **7.1 Baseline characteristics**

1514 Baseline characteristics are collected prior to inclusion and randomization with respect to the
1515 following baseline characteristics: demographic details and patient characteristics, such as
1516 gestational age, small for gestational age, antenatal problems, antenatal steroids, surfactant
1517 therapy, mode of delivery, resuscitation details, Apgar scores, presence of IVH/PVL, and
1518 occurrence of PDA. Base line characteristics on ventilator settings, gas exchange will be
1519 collected on day of randomization.

1520

1521 **7.2 Co-interventions**

1522 Timing, dose and duration of all co-interventions, such as methylxanthines, diuretics,
1523 bronchodilators/inhalation corticosteroids and inhaled nitric oxide, as well as the ventilation
1524 mode with the ventilator settings will be recorded and analyzed.

1525

1526 **7.3 Statistical analysis**

1527 Normally distributed data will be presented as mean \pm standard deviations, not-normally
1528 distributed data as medians and (interquartile) ranges. Categorical data will be analysed
1529 using the Chi-square test. Continuous data will be analysed using the Student's *t* test or
1530 Mann-Whitney test as appropriate. Both intention-to-treat and per-protocol analysis will be
1531 employed. The effect of hydrocortisone on the primary outcome death or BPD will be
1532 assessed by multi-variable logistic regression analysis including possible confounders.
1533 Statistical significance is set at $p < 0.05$.

1534

1535 **8. SAFETY REPORTING**

1536 **8.1 Section 10 WMO (Wet Medisch-wetenschappelijk Onderzoek met Mensen)**

1537 In accordance to section 10, subsection 1, of the Dutch WMO, the investigator will inform the
1538 subjects and the reviewing accredited METC (*Medisch Ethische Toetsingscommissie*) if
1539 anything occurs, on the basis of which it appears that the disadvantages of participation may
1540 be significantly greater than was foreseen in the research proposal. The study will be
1541 suspended pending further review by the accredited METC, except insofar as suspension
1542 would jeopardise the subjects' health. The investigator will take care that all subjects are kept
1543 informed.

1544

1545 **8.2 Adverse and serious adverse events (SAE)**

1546 Adverse events are defined as any undesirable experience occurring to a subject during a
1547 clinical trial, whether or not considered related to the investigational drug. All adverse
1548 events reported spontaneously by the subject's parents or caregivers or observed by the
1549 investigator or his staff will be recorded. A **serious adverse event** is any untoward medical
1550 occurrence or effect that at any dose
1551 - results in death;
1552 - is life threatening (at the time of the event);
1553 - requires hospitalization or prolongation of existing inpatients' hospitalization;
1554 - results in persistent or significant disability or incapacity;
1555 - is a congenital anomaly or birth defect (not applicable in this trial);
1556 - is a new event of the trial likely to affect the safety of the subjects, such as an unexpected
1557 outcome of an adverse reaction, lack of efficacy of an IMP used for the treatment of a life
1558 threatening disease, major safety finding from a newly completed animal study, etc.
1559 All SAEs will be reported to the Data Monitoring Committee and to the accredited METC that
1560 approved the protocol, according to the requirements of that METC.

1561 **8.2.1 Suspected unexpected serious adverse reactions (SUSAR)**

1562 Adverse reactions are all untoward and unintended responses to an investigational product
1563 related to any dose administered.

1564

1565 Unexpected adverse reactions are adverse reactions, of which the nature, or severity, is not
1566 consistent with the applicable product information (e.g. Investigator's Brochure for an
1567 unapproved IMP or Summary of Product Characteristics (SPC) for an authorised medicinal
1568 product).

1569

1570 The Steering Committee will report expedited the following SUSARs through the web portal

1571 *ToetsingOnline* to the METC:

1572 – SUSARs that have arisen in the clinical trial that was assessed by the METC;

1573 – SUSARs that have arisen in other clinical trials of the same sponsor and with the same

1574 medicinal product, and that could have consequences for the safety of the subjects

1575 involved in the clinical trial that was assessed by the METC.

1576 The remaining SUSARs are recorded in an overview list (line-listing) that will be submitted

1577 once every half year to the METC. This line-listing provides an overview of all SUSARs from

1578 the study medicine, accompanied by a brief report highlighting the main points of concern.

1579 The expedited reporting of SUSARs through the web portal *ToetsingOnline* is sufficient as

1580 notification to the competent authority.

1581

1582 The Steering Committee will report expedited all SUSARs to the competent authorities in

1583 other Member States, according to the requirements of the Member States.

1584

1585 The expedited reporting will occur not later than 15 days after the Steering Committee has

1586 first knowledge of the adverse reactions. For fatal or life threatening cases the term will be

1587 maximal 7 days for a preliminary report with another 8 days for completion of the report.

1588

1589 **8.2.2 Annual safety report**

1590 In addition to the expedited reporting of SUSARs, the Steering Committee will submit, once a

1591 year throughout the clinical trial, a safety report to the accredited METC, competent

1592 authority, Medicine Evaluation Board and competent authorities of the concerned Member

1593 States.

1594 This safety report consists of:

- 1595 – a list of all suspected (unexpected or expected) serious adverse reactions, along with an
- 1596 aggregated summary table of all reported serious adverse reactions, ordered by organ
- 1597 system, per study;
- 1598 – a report concerning the safety of the subjects, consisting of a complete safety analysis
- 1599 and an evaluation of the balance between the efficacy and the harmfulness of the
- 1600 medicine under investigation.

1601

1602 **8.3 Follow-up of adverse events**

1603 All adverse events will be followed until they have abated, or until a stable situation has

1604 been reached. Depending on the event, follow up may require additional tests or medical

1605 procedures as indicated, and/or referral to the general physician or a medical specialist. All

1606 infants will participate in the usual NICU follow-up program. This program is targeted at

1607 evaluating and coordinating diagnostic procedures and treatment of all prematurity related

1608 problems, in close cooperation with regional and local pediatricians.

1609

1610 **8.4 Data Monitoring Committee (DMC)**

1611 An external Data Monitoring Committee (DMC) will conduct reviews of patient safety

1612 presented initially on hydrocortisone vs. placebo basis. Data summaries for the DMC will be

1613 prepared by a statistician who is not a member of the investigating team. Formal interim

1614 analyses will be conducted when approximately 25%, 50% and 75% of the anticipated

1615 outcome data are available. The DMC will have access to all safety data and will be in a

1616 position to make recommendations to the trial's Steering Committee - should a risk to the

1617 safety of participants arise. This safety data will include, but not be restricted to, serious

1618 adverse events and the safety outcomes listed as secondary outcomes. The results of the
1619 interim analyses will remain confidential – only the unblinded statistician will have access to
1620 the unblinded analyses. If the DMC recommends modification or cessation of the study
1621 protocol, this will be discussed with the Steering Committee, who will make the decision.
1622 The DMC will be composed of 5 individuals with expertise and extensive experience in
1623 newborn ventilation, trial management or statistics. The Steering Committee will propose a
1624 detailed mandate and review this with the DMC, from the outset. None of the members will
1625 be from institutions represented in the study. The DMC will report to the Steering
1626 Committee with whom the onus of early closure will ultimately reside. Both the DMC and
1627 the Steering Committee will be informed on the implications of recent information on
1628 premature stopping of trials.

1629

1630 **9. ETHICAL CONSIDERATIONS**

1631 **9.1 Regulation statement**

1632 The study will be conducted according to the principles of the Declaration of Helsinki⁵³ and
1633 in accordance with the Medical Research Involving Human Subjects Act (WMO).

1634

1635 **9.2 Recruitment and informed consent**

1636 Patients will be recruited and their parents will be informed and asked for consent by the
1637 attending paediatricians. Informed written consent must be obtained from the parents prior to
1638 randomisation for the study. The patient information letter and informed consent are provided
1639 in section I of the study dossier. The right of a parent or patient to refuse participation without
1640 giving reasons will be respected. The parents will remain free to withdraw their child at any
1641 time from the study without consequences for further treatment.

1642

1643 **9.3 Benefits and risks assessment, group relatedness**

1644 Burden: All infants participating in (either treatment arm of) the study are subjected to
1645 routine neonatal intensive care. The administration of the study intervention itself
1646 (hydrocortisone or placebo administration) does not pose an extra burden on the patients.
1647 This study does not require extra investigations or interventions.

1648 Benefit and risks: Hydrocortisone may facilitate extubation and thereby reduce the total
1649 duration of mechanical ventilation. In addition, hydrocortisone may reduce the incidence of
1650 BPD. Both these beneficial effects may improve neurodevelopmental outcome. On the other
1651 hand, use of hydrocortisone may increase the risk for hyperglycemia, hypertension, systemic
1652 infection, gastrointestinal perforation and a delay in neurodevelopment. However,
1653 gastrointestinal perforation and delayed neurodevelopment have only been reported in
1654 studies administering corticosteroids in the first week of life and/or in combination with
1655 other medication. In this study the risk of gastrointestinal perforation and delayed
1656 neurodevelopment may be reduced because hydrocortisone will be administered after the
1657 first week of life and will not be combined with other drugs that are known to increase the
1658 risk for these adverse effects. Infants assigned to the placebo group will not benefit from the
1659 aforementioned possible beneficial effects nor be subjected to the possible adverse effect of
1660 hydrocortisone.

1661 Group relatedness: BPD is a complication occurring exclusively in preterm infants. Any
1662 intervention aiming to reduce the risk of this complication therefore needs to be studied in
1663 this specific population at risk.

1664

1665 **9.4 Compensation for injury**

1666 The sponsor/investigator has a liability insurance which is in accordance with article 7,
1667 subsection 6 of the WMO. The sponsor (also) has an insurance which is in accordance with
1668 the legal requirements in the Netherlands (Article 7 WMO and the Measure regarding
1669 Compulsory Insurance for Clinical Research in Humans of 23rd June 2003). This insurance
1670 provides cover for damage to research subjects through injury or death caused by the study.
1671 1. € 450.000,-- (i.e. four hundred and fifty thousand Euro) for death or injury for each
1672 subject who participates in the Research;
1673 2. € 3.500.000,-- (i.e. three million five hundred thousand Euro) for death or injury for all
1674 subjects who participate in the Research;
1675 3. € 5.000.000,-- (i.e. five million Euro) for the total damage incurred by the organization
1676 for all damage disclosed by scientific research for the Sponsor as ‘verrichter’ in the
1677 meaning of said Act in each year of insurance coverage.
1678 The insurance applies to the damage that becomes apparent during the study or within 4 years
1679 after the end of the study.

1680

1681 **9.5 Incentives**

1682 Participants will not receive a financial compensation for participation as an incentive.

1683

1684 **10. ADMINISTRATIVE ASPECTS AND PUBLICATION**

1685 **10.1 Handling and storage of data and documents**

1686 Datamanagement will be implemented according to Good Clinical Practice (GCP)-guidelines.

1687 Patient data will be entered by way of an eCRF in a central GCP proof internet based

1688 database to facilitate on-site data-entry. Security is guaranteed with login names, login

1689 codes and encrypted data transfer. An experienced datamanager will maintain the database

1690 and check the information in the database for completeness, consistency and plausibility.

1691

1692 The data of all subjects will be coded and this coding will not be retraceable to the individual
1693 patient. The key to this coding is safeguarded by the investigator. A limited number of
1694 people have access to the source data. These are the principal investigator, investigating
1695 doctor and investigating personnel. Personal data are only processed by the researchers or
1696 by those who fall directly under their authority. In addition, the study monitor, quality
1697 assurance auditor, employees from the METC and the Health Care Inspectorate of the
1698 Ministry of Health, welfare and Sport (Nederlandse Inspectie voor de Gezondheidszorg) have
1699 access to the source data. All are subject to the pledge of confidentiality. Data and human
1700 material will be stored for 15 years strictly confidential.

1701

1702 **10.2 Amendments**

1703 Amendments are changes made to the trial after a favourable opinion by the accredited METC
1704 has been given. All amendments will be notified to the METC that gave a favourable opinion.
1705 All substantial amendments will be notified to the METC and to the competent authority.
1706 Non-substantial amendments will not be notified to the accredited METC and the competent
1707 authority, but will be recorded and filed by the Steering Committee.

1708

1709 **10.3 Annual progress report**

1710 If requested, an annual progress report of the progress of the trial will be provided to the
1711 accredited METC. Information will be provided on the date of inclusion of the first subject,
1712 numbers of subjects included and numbers of subjects that have completed the trial, serious
1713 adverse events/ serious adverse reactions, other problems, and amendments. In case the study
1714 is ended prematurely, the investigator will notify the accredited METC, including the reasons
1715 for the premature termination. Within one year after the end of the study, the

1716 investigator/sponsor will submit a final study report with the results of the study, including
1717 any publications/abstracts of the study, to the accredited METC.

1718

1719 **10.4 Public disclosure and publication policy**

1720 The study will be registered in the EUDRACT, the website of the Dutch National Competent
1721 Authority, the 'Centrale Commissie Mensgebonden Onderzoek' (CCMO), Dutch public trial
1722 registry, part of the WHO registry. The results of the study will be published in peer-
1723 reviewed international medical journals. In addition, the results of the study will be used for
1724 development and implementation of a guideline on treatment of BPD, which will benefit
1725 future patients.

1726

1727 **11. Organisation**

1728 Steering Committee

1729 The Steering Committee is the main policy and decision making committee of the study and
1730 has final responsibility for the scientific conduct of the study. It will be composed of
1731 representatives of the sponsors, of the investigators of the participating centres and of the
1732 MCRN. The specific tasks of the Steering Committee are:

- 1733 • Approve the study protocol
- 1734 • Approve necessary changes in the protocol based on considerations of feasibility
- 1735 • Act upon recommendations of the Data Monitoring Committee
- 1736 • Review performance reports of the study sites
- 1737 • Resolve operational problems brought before it by the project manager
- 1738 • Approve study reports and papers for publication.

1739

1740 Data Monitoring Committee

1741 An independent Data Monitoring Committee (DMC) will be created specifically for this trial.

1742 The DMC will act in advisory capacity to the Steering Committee . See Paragraph 8.4 for a

1743 description of the membership, tasks and responsibilities of the DMC.

1744

1745 Clinical Project Manager / Central Study Coordinator

1746 An experienced clinical project manager (CPM) from MCRN will manage the quality of the

1747 study according to the Good Clinical Practice (GCP)-guidelines, supervise the data monitoring

1748 process, and verify the quality of conduct of all study personnel. The CPM and/or clinical

1749 research associate (CRA) will arrange that the study personnel is adequately trained in GCP

1750 and study protocol, where needed. The CPM meets regularly with the CRA, data managers,

1751 the Data Safety Monitoring Committee (DSMC), financial departments of study centers, and

1752 all other relevant parties to assure study progress, quality and financials are according to

1753 planning. The CPM will coordinate regulatory authority and ethics committee submissions.

1754 The CPM provides regularly an overall study status report to the Steering Committee

1755

1756 Study Monitoring

1757 The study will be monitored by an experienced monitor from MCRN throughout its duration

1758 by means of personal visits to the Investigator's facilities and through other communications

1759 (e.g., telephone calls, written correspondence).

1760 Monitoring visits will be scheduled at mutually agreeable times periodically throughout the

1761 study and at frequency deemed appropriate for the study.

1762 These visits will be conducted to evaluate the progress of the study, ensure the rights and

1763 wellbeing of the subjects are protected, check that the reported clinical study data are

1764 accurate, complete and verifiable from source documents, and the conduct of the study is in

1765 compliance with the approved protocol and amendments, GCP and applicable national
1766 regulatory requirements. A monitoring visit will include a review of the essential clinical
1767 study documents (regulatory documents, CRFs, source documents, drug disposition records,
1768 subject informed consent forms, etc.) as well as discussion on the conduct of the study with
1769 the Investigator and staff. The Investigator and staff should be available during these visits to
1770 facilitate the review of the clinical study records and resolve/document any discrepancies
1771 found during the visit.

1772

1773 Quality Assurance Audits and Inspections

1774 The Sponsor's (or an authorized representative's) Quality Assurance department may conduct
1775 audits of all aspects of the clinical study either during the study or after the study has been
1776 completed. By participating this trial the investigator agree to this requirement.

1777 The clinical study may also be subject to inspection by regulatory authorities as well as the
1778 accredited Medical Ethical Committee/ Competent authority to ascertain that the study is
1779 being or has been conducted in accordance with protocol requirements, GCP, as well as the
1780 applicable regulatory requirements.

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1786 12. REFERENCES

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- 1944
- 1945

1946 **APPENDIX 1**

1947

**Afdeling Neonatologie**

1955

STUDIE MEDICATIE SCHEMA

1956

1957 **voor:** **[Klik hier en typ naam]**1958 **geboren op:** **[Klik hier en typ geboortedatum]**

1959

Gewicht: kg.
startdatum:

| | Dagdosis per lichaamsgewicht | Frequentie | mg/dosis | | Dagdosis per lichaamsgewicht | Frequentie | mg/dosis |
|------------------|---------------------------------|------------|----------|------------------|---------------------------------|------------|----------|
| 3-jan-11 | 5 mg/kg/dg | 4 x | 0 mg. | 15-jan-11 | 2.5 mg/kg/dg | 2 x | 0 mg. |
| 4-jan-11 | 5 mg/kg/dg | 4 x | 0 mg. | 16-jan-11 | 2.5 mg/kg/dg | 2 x | 0 mg. |
| 5-jan-11 | 5 mg/kg/dg | 4 x | 0 mg. | 17-jan-11 | 2.5 mg/kg/dg | 2 x | 0 mg. |
| 6-jan-11 | 5 mg/kg/dg | 4 x | 0 mg. | 18-jan-11 | 2.5 mg/kg/dg | 2 x | 0 mg. |
| 7-jan-11 | 5 mg/kg/dg | 4 x | 0 mg. | 19-jan-11 | 2.5 mg/kg/dg | 2 x | 0 mg. |
| 8-jan-11 | 5 mg/kg/dg | 4 x | 0 mg. | 20-jan-11 | 1.25 mg/kg/dg | 1 x | 0 mg. |
| 9-jan-11 | 5 mg/kg/dg | 4 x | 0 mg. | 21-jan-11 | 1.25 mg/kg/dg | 1 x | 0 mg. |
| 10-jan-11 | 3.75 mg/kg/dg | 3 x | 0 mg. | 22-jan-11 | 1.25 mg/kg/dg | 1 x | 0 mg. |
| 11-jan-11 | 3.75 mg/kg/dg | 3 x | 0 mg. | 23-jan-11 | 1.25 mg/kg/dg | 1 x | 0 mg. |
| 12-jan-11 | 3.75 mg/kg/dg | 3 x | 0 mg. | 24-jan-11 | 1.25 mg/kg/dg | 1 x | 0 mg. |
| 13-jan-11 | 3.75 mg/kg/dg | 3 x | 0 mg. | | | | |
| 14-jan-11 | 3.75 mg/kg/dg | 3 x | 0 mg. | | | | |

1960

1961

1962

1963 **Opmerkingen:** **[Klik hier en typ opmerkingen]**

1964

1965 **Naam arts:** **[Klik hier en typ naam arts]**1966 **sein:** **[Klik hier en typ seinnummer]**

1967

1968 **Paraaf:**

1969

1970

1971

1972

1973 **APPENDIX 2**

1974

1975 **Oxygen reduction test**

1976 Bronchopulmonary dysplasia (BPD) can be classified in to mild, moderate or severe

1977 depending on the amount and duration of supplemental oxygen and the level of respiratory

1978 support. If a patient has received supplemental oxygen for more than 28 d ($FiO_2 > 0.21$ for

1979 more than 12 hours each day) and is receiving no extra oxygen at 36 weeks postmenstrual

1980 age (PMA), he or she is classified as having mild BPD. If the oxygen need at 36 weeks PMA is

1981 between 0.21 and 0.30, BPD is classified as moderate and in case of a $FiO_2 > 0.30$ and/or

1982 receiving continuous positive airway pressure (nCPAP)/mechanical ventilation as severe.

1983 It is important to realize that the duration of supplemental oxygen is highly dependent on

1984 target ranges of transcutaneous oxygen saturation (SpO_2) and the alertness of the clinician

1985 to actively wean oxygen delivery.

1986 To make sure that patients receive supplemental oxygen for pulmonary reasons and to

1987 standardize the amount of oxygen to predefined and uniform SpO_2 targets, Walsh et al.

1988 developed a so-called oxygen reduction test at 36 weeks PMA. Patients are eligible for

1989 testing if they need a FiO_2 between 0.21 and 0.30 to maintain the SpO_2 between 90-96% **or** if1990 they receive a $FiO_2 > 0.30$ resulting in a $SpO_2 > 96\%$. Patients supported with nasal cannulae

1991 (flow not nCPAP) without supplemental oxygen, and patients treated with

1992 nCPAP/mechanical ventilation or with a $FiO_2 > 0.30$ resulting in a $SpO_2 < 96\%$ do not need

1993 additional testing, and are, respectively, classified as having mild and severe BPD.

1994 ***The oxygen reduction test***1995 **Indications:**

1996 - $\text{FiO}_2 > 0.21$ and < 0.30 with oxygen saturation ranges between 90% and 96%

1997 - $\text{FiO}_2 > 0.30$ with a oxygen saturation range above 96%

1998 Methods:

1999 The patient is placed in supine position and the test is initiated 30 minutes after a feeding. The

2000 supplemental oxygen requirement will be gradually weaned to room air while monitoring

2001 SpO_2 . The diagnosis moderate BPD can be rejected when the SpO_2 remain above $\geq 88\%$ in

2002 room air during 1 hour without apnea or bradycardia.

2003 The diagnosis moderate BPD is confirmed if the saturation goes below 80% during > 1 minute

2004 or remains between 80-87% during > 5 minutes. All occurrences of movement artifact

2005 (defined as visible motion of the infant together with loss of plethysmograph signal from the

2006 monitor) are recorded and corresponding saturation values are to be deleted.

2007

2008 The test contains 4 phases

2009 Phase 1: Baseline evaluation

2010 For 15 minutes heart rate, respiratory rate, SpO_2 , number of apnea (cessation of breathing $>$

2011 20 seconds) and bradycardia (heart rate $< 80/\text{min}$ during > 10 sec) will be collected.

2012 Phase 2: Oxygen reduction

2013 The supplemental oxygen will be weaned by 2% to room air, after which the flow will be

2014 weaned with 0.1 L/min to 0 L/min; The nasal cannulae will be removed from the nares, but

2015 not removed from the face.

2016 Phase 3: Observation period

2017 For the period of 1 hour the heart rate, respiratory rate, and SpO_2 in room air will be

2018 registered. In case of a desaturation below 80% for > 1 minute or saturation between 80-87%

2019 for > 5 minutes, the supplemental oxygen will be restarted and the test will be aborted.

2020 *Phase 4: Back to situation before the test*

2021 The level of supplemental oxygen and flow will be reset to the status before the test.

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2068 PROTOCOL

2069 **Systemic Hydrocortisone To Prevent Bronchopulmonary Dysplasia in preterm**2070 **infants: the SToP-BPD study**2071 **A multicenter randomised placebo controlled trial**

| | |
|-------------------------------|---|
| Protocol ID | Systemic Hydrocortisone To Prevent Bronchopulmonary Dysplasia in preterm infants: the SToP-BPD study |
| Short title | Hydrocortisone for bronchopulmonary dysplasia |
| Version | 3 |
| Date | 16 mei 2011 |
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2144 **LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS**

2145

| | | |
|------|---------|--|
| 2146 | ARR | Absolute Risk Reduction |
| 2147 | BPD | BronchoPulmonary Dysplasia |
| 2148 | BW | Birth Weight |
| 2149 | CDP | Continuous Distension Pressure |
| 2150 | CGA | Corrected Gestational Age |
| 2151 | CP | Cerebral Palsy |
| 2152 | DNRN | Dutch Neonatal Research Netwerk; in Dutch: Nederlands Neonataal |
| 2153 | | Research Netwerk (NNRN) |
| 2154 | DMC | Data Monitoring & Safety Committee |
| 2155 | ESEMC | External Safety and Efficacy Monitoring Committee |
| 2156 | GA | Gestational Age |
| 2157 | HFO | High Frequency Oscillation |
| 2158 | IMP | Investigational Medicinal Product |
| 2159 | IVH | IntraVentricular Haemorrhage |
| 2160 | MAwP | Mean Airway Pressure |
| 2161 | METC | Medical research ethics committee (MREC); in Dutch: Medisch |
| 2162 | | Ethische Toetsing Commissie |
| 2163 | MRI | Magnetic Resonance Imaging |
| 2164 | NEC | Necrotising EnteroColitis |
| 2165 | NICU | Neonatal Intensive Care Unit |
| 2166 | NICHD | National Institutes for Child Health and Human Development |
| 2167 | NNT | Number Needed to Treat |
| 2168 | NVK | Dutch Society of Pediatricians; in Dutch: Nederlandse Vereniging voor |
| 2169 | | Kindergeneeskunde |
| 2170 | PDA | Persistent Ductus Arteriosus |
| 2171 | PMA | PostMenstrual Age |
| 2172 | PNA | PostNatal Age |
| 2173 | PVL | PeriVentricular Leucomalacia |
| 2174 | RCT | Randomised Controlled Trial |
| 2175 | RI | Respiratory Index |
| 2176 | SAE | Serious Adverse Event |
| 2177 | SD | Standard Deviation |
| 2178 | Sponsor | The sponsor is the party that commissions the organisation of |
| 2179 | | performance of the research, for example a pharmaceutical company, |
| 2180 | | academic hospital, scientific organisation or investigator. A party that |
| 2181 | | provides funding for a study but does not commission it is not |
| 2182 | | regarded as the sponsor, but referred to as a subsidising party. |
| 2183 | VLBW | Very Low Birth Weight |
| 2184 | WMO | Medical Research Involving Human Subjects Act; in Dutch: Wet |
| 2185 | | Medisch-wetenschappelijk Onderzoek met Mensen |
| 2186 | | |

2187

2188 **SUMMARY**

2189 **Background:** Randomised controlled trials (RCTs) have shown that treatment of chronically
2190 ventilated preterm infants after the first week of life with dexamethasone reduces the
2191 incidence of bronchopulmonary dysplasia (BPD). However, there are concerns that its use
2192 may increase the risk of adverse neurodevelopmental outcome. Hydrocortisone has been
2193 suggested as an alternative therapy. So far no RCT has investigated its efficacy when
2194 administered after the first week of life to ventilated preterm infants.

2195 **Objective:** To establish the efficacy of hydrocortisone given after one week of life to reduce
2196 the incidence of the combined outcome death or BPD in chronically ventilated preterm
2197 infants.

2198 **Study design:** Randomised double blind placebo controlled multicenter study.

2199 **Study population:** Very low birth weight infants (GA<30weeks and/or BW<1250grams),
2200 ventilator dependent at a postnatal age of 7 – 14 days.

2201 **Intervention:** Administration of hydrocortisone or placebo during a 22 day tapering
2202 schedule.

2203 **Outcome parameters:** Primary outcome measure is survival free of BPD at 36 weeks
2204 postmenstrual age (PMA). Secondary outcomes are short term effects on the pulmonary
2205 condition, adverse effects during hospitalization, and long-term neurodevelopmental
2206 sequelae assessed at 2 years corrected gestational age (CGA).

2207 **Burden, benefit and risks associated with participation; group relatedness:**

2208 Burden: All infants participating in (either treatment arm of) the study are subjected to
2209 routine neonatal intensive care. The administration of the study intervention itself
2210 (hydrocortisone or placebo administration) does not pose an extra burden on the patients.
2211 This study does not require extra investigations or interventions.

2212 Benefit and risks: Hydrocortisone may facilitate extubation and thereby reduce the total
2213 duration of mechanical ventilation. In addition, hydrocortisone may reduce the incidence of
2214 BPD. Both these beneficial effects may improve neurodevelopmental outcome. On the other
2215 hand, use of hydrocortisone may increase the risk for hyperglycaemia, hypertension,
2216 systemic infection, gastrointestinal perforation and a delay in neurodevelopment. However,
2217 gastrointestinal perforation and delayed neurodevelopment have only been reported in
2218 studies administering corticosteroids in the first week of life and/or during combinations
2219 with other medication. In this study the risk of gastrointestinal perforation and delayed
2220 neurodevelopment may be reduced because hydrocortisone will be administered after the
2221 first week of life and combinations with other drugs will be avoided as much as possible.
2222 Infants assigned to the placebo group will not benefit from the aforementioned possible
2223 beneficial effects nor be subjected to the possible adverse effect of hydrocortisone.
2224 Group relatedness: BPD is a complication occurring exclusively in preterm infants. Any
2225 intervention aiming to reduce the risk of this complication therefore needs to be studied in
2226 this specific population at risk.

2227 **1. BACKGROUND**

2228 Bronchopulmonary dysplasia (BPD) is the most common complication of premature birth,
2229 with a reported incidence of 8% to 35%.^{1,2} BPD is characterized by chronic respiratory
2230 distress, the need for prolonged respiratory support, an increased risk of recurrent
2231 pulmonary infections, airway hyperreactivity during the first years of life³ and life-long
2232 alterations in lung function.⁴⁻⁶ Patients with established BPD have high rates of readmissions
2233 and utilization of health services resulting in tremendous societal costs compared to children
2234 without BPD.⁷⁻⁹ Furthermore, BPD is considered an important risk factor for adverse
2235 neurodevelopmental outcome after premature birth¹⁰⁻¹⁴ with life-long economic and social
2236 consequences.¹⁵⁻¹⁸

2237

2238 In addition to direct mechanical injury, caused by artificial ventilation and oxygen toxicity,
2239 pulmonary inflammation has been identified as an important mediator in the development
2240 of BPD.¹⁹⁻²¹ This is the rationale for treating patients with glucocorticoids, a well known anti-
2241 inflammatory agent. Randomised controlled trials (RCTs) summarized in several systematic
2242 reviews have shown that postnatal systemic glucocorticoids, mainly dexamethasone, reduce
2243 the risk of the combined outcome death or BPD in ventilated preterm infants.²²⁻²⁴
2244 Furthermore, systemic glucocorticoids seem to be most effective when administered in a
2245 time frame of 7 to 14 days postnatal age, the so-called moderately early treatment
2246 onset.^{25,26} However, initiating dexamethasone treatment in the first days of life seems to be
2247 associated with an increased the risk of cerebral palsy (CP). Although this complication has
2248 not been reported by RCTs investigating dexamethasone treatment initiated after the first
2249 week of life, these alarming reports have resulted in a general concern on the use of
2250 dexamethasone in preterm infants.²⁷⁻²⁹ Based on this concern, the American Academy of

2251 Pediatrics, Canadian Paediatric Society, and the European Association of Perinatal Medicine
2252 have stated that clinical trials should be performed to investigate the use of alternative anti-
2253 inflammatory glucocorticoids, such as the less potent glucocorticoid hydrocortisone.^{30,31}
2254
2255 Despite the ongoing concerns on their use, systemic glucocorticoids are still used in
2256 approximately 10% of the preterm infants at risk for BPD.³²⁻³⁴ Dexamethasone is still the
2257 most widely used glucocorticoid drug, but its dose has been significantly reduced and
2258 administration is often postponed until the 3rd or 4th week of life.²⁷
2259
2260 As an alternative, many clinicians have started to use hydrocortisone. Animal data suggest
2261 that hydrocortisone has a less detrimental effect on the brain than dexamethasone.³⁵
2262 However, no placebo controlled RCT has investigated the use of hydrocortisone after the
2263 first week in life in ventilator dependent preterm infants.³⁶ Six RCTs investigating a low
2264 hydrocortisone dose started within < 72 hours after birth (early treatment) failed to show a
2265 clear reduction in the incidence of BPD.³⁷⁻⁴² Only one of these trials reported long-term
2266 follow-up, showing no differences in adverse neurodevelopmental sequelae.⁴³ These
2267 findings are supported by several historical cohort studies, showing no increased risk of
2268 adverse neurodevelopmental outcome in hydrocortisone treated infants.⁴⁴⁻⁴⁶
2269
2270 In most Dutch Neonatal Intensive Care Units (NICUs) preterm infants who are ventilator-
2271 dependent in the second week of life are no longer treated with glucocorticoids. Infants are
2272 kept on the ventilator allowing spontaneous recovery of lung function over time, sometimes
2273 supported by other interventions, such as diuretics and inhalation therapy. With this
2274 approach, some infants can be successfully weaned and extubated. Only those infants that

2275 remain ventilator dependent after 3-4 weeks are treated with glucocorticoids, with the
2276 primary objective to wean and extubate.

2277 Although this approach will undoubtedly result in successful extubation of most infants with
2278 the lowest possible use of glucocorticoids, the question remains if this is also the best
2279 strategy in reducing the incidence of BPD in preterm infants ventilated after 7 days of life.
2280 This question seems justified and relevant because BPD, and not failure to extubate, is
2281 associated with adverse medium- and long-term outcome. This is the main reason why the
2282 primary outcome of this study is death or BPD and not failure to extubate.

2283

2284 The NICU at the University Medical Center Utrecht has historically used hydrocortisone for
2285 chronically ventilated preterm infants. Retrospective studies seem to indicate that
2286 hydrocortisone is effective in reducing BPD, without causing serious adverse effects.
2287 However, these findings need to be confirmed or refuted by a large randomized placebo
2288 controlled trial. Despite the absence of randomized evidence, three out of the 10 Dutch
2289 NICUs switched from dexamethasone to hydrocortisone. This diversity in treatment between
2290 NICUs is undesirable and has also been debated in the public press.⁴⁷ As a first step to
2291 resolve this diversity in treatment, all 10 Dutch NICUs have indicated that a RCT comparing
2292 hydrocortisone with placebo is urgently needed, an initiative that is also supported by the
2293 Dutch Society of Pediatricians (NVK), giving such a trial top priority. Since the NICUs which
2294 already use hydrocortisone are reluctant or refuse to prescribe dexamethasone as trial
2295 medication, a RCT comparing dexamethasone versus hydrocortisone is not possible.

2296

2297 The optimal dose of hydrocortisone is currently unknown. However, the NICU in Utrecht has
2298 been using a fixed hydrocortisone treatment regimen for several decades now and this

2299 regimen has also been adopted by the other Dutch NICUs using hydrocortisone.
2300 Retrospective studies strongly suggest that this is a safe dose, because it was not associated
2301 with an increased risk of adverse neurological outcome.^{45,48} Comparing hydrocortisone
2302 treated patients with dexamethasone treated patients in other NICUs showed no difference
2303 in the incidence of BPD, suggesting that this dose is equally effective in reducing BPD.⁴⁸
2304 Based on these findings and current clinical practice, we decided to adopt the dosing
2305 regimen from Utrecht for this study.

2306

2307 Based on the current available evidence, the American Academy of Pediatrics has concluded
2308 that: (1) routine use of systemic dexamethasone for the prevention or treatment of CLD in
2309 infants with VLBW is not recommended; (2) outside the context of a randomized, controlled
2310 trial, the use of corticosteroids should be limited to exceptional clinical circumstances. Based
2311 on these recommendation ventilated preterm infants are no longer routinely treated with
2312 postnatal corticosteroids. Furthermore, in exceptional cases treatment is, in most cases,
2313 postponed until after the third week of life. Comparison of hydrocortisone to a placebo is
2314 therefore warranted because standard therapy in the second week of life (7-14 d after birth)
2315 is to wait for spontaneous recovery of lung function. In exceptional clinical circumstances
2316 treatment with a (rescue) open label glucocorticoids is still possible in the current study.
2317 Although based on the above, the *extra* risks for the patients in this study are probably
2318 limited, a data monitoring committee will closely monitor any possible adverse effects and
2319 risks, as also explained in paragraph 9.4.

2320

2321 **2. OBJECTIVE**

2322 To investigate if hydrocortisone is safe and effective in reducing the incidence of the
2323 combined outcome death or BPD at 36 weeks PMA in chronically ventilated preterm infants,
2324 as compared to placebo. This study **does not** aim to successfully extubate ventilator-
2325 dependent preterm infants with the lowest possible use of glucocorticoids (i.e.
2326 hydrocortisone), but to use glucocorticoids as an early intervention (7-14 d after birth) to
2327 reduce the risk of death or BPD in these ventilator-dependent preterm infants. From this
2328 point of view the treatment strategy is fundamentally different from what is currently used
2329 in daily clinical practice.

2330

2331 **3. STUDY DESIGN**

2332 Multicenter randomised double-blind placebo-controlled trial with a total duration of 5 years
2333 conducted in 15 neonatal intensive care units in the Netherlands (n=10) and Belgium (n=5).

2334

2335 **4. STUDY POPULATION**

2336 **4.1 Population eligibility**

2337 Ventilated VLBW infants at high risk for BPD treated in a level III NICU

2338

2339 **4.2 Inclusion criteria**

2340 Preterm infants with:

- 2341 - a gestational age < 30 wks and/or birth weight < 1250 g
- 2342 - ventilator dependency at 7-14 days PNA
- 2343 - a respiratory index (RI = MAwP x FiO₂) of ≥ 3.5 for more than 12 h/day for at least
2344 48 hours, ensuring adequate oxygen saturation (85-95%) and pCO₂ values in
2345 premature infants (5.0-7.5 kPa).

2346 Note: these targets are used to ensure homogeneous assessment of MAwP and FiO₂ for
2347 patient inclusion among participating centres. After inclusion of the patient in the
2348 study, physicians are free to use local targets for oxygenation and ventilation.

2349

2350 **4.3 Exclusion criteria**

2351 - chromosomal defects (e.g. trisomy 13, 18, 21)

2352 - major **congenital** malformations that:

2353 ○ compromise lung function (e.g. surfactant protein deficiencies, congenital

2354 diaphragmatic hernia)

2355 ○ result in chronic ventilation (e.g. Pierre Robin sequence)

2356 ○ increase the risk of death or adverse neurodevelopmental outcome

2357 (congenital cerebral malformations)

2358 Note: intraventricular haemorrhages, periventricular leucomalacia and

2359 cerebral infarction are not considered **congenital** malformations and

2360 therefore are no exclusion criteria.

2361 - Use of dexamethasone or hydrocortisone for the sole purpose of improving lung

2362 function and respiratory status prior to inclusion

2363

2364 Considerations

2365 Although (suspected or proven) sepsis, pneumonia, necrotizing enterocolitis (NEC) and

2366 patent ductus arteriosus (PDA) are well-known causes of respiratory failure, these diagnoses

2367 are known to be independent risk factors for developing BPD. Therefore, these diagnoses are

2368 **not** considered to be exclusion criteria. The following should be taken into consideration:

2369 7. In ventilator-dependent cases of sepsis and pneumonia the attending physician may
2370 start antibiotics and await the effect on respiratory drive/ pulmonary status for 48
2371 hours. If the patient meets the inclusion criteria after 48 h, he/she is eligible for
2372 inclusion.

2373 8. *Trials studying the early use (initiated < 96 hours after birth) of corticosteroids have*
2374 *shown that treatment with corticosteroids may increase the risk of intestinal*
2375 *perforation. Speculating on the pathogenesis of this adverse effect, it has been*
2376 *suggested that the synchronous use of indomethacin and corticosteroids might*
2377 *explain this finding. However, trials starting dexamethasone between 7-14 d after life*
2378 *have **not** reported an increased risk of intestinal perforation, despite the fact that*
2379 *some of these patients were also treated for hemodynamically significant PDA with*
2380 *indomethacin. In other words, the evidence for a possible adverse effect of the*
2381 *combined use of corticosteroids and indomethacin/ibuprofen is weak. For this reason*
2382 *the combined use of corticosteroids and indomethacin/ibuprofen is **NOT** prohibited*
2383 *within the STOP-BPD trial. However, where possible in the time window of 7-14 days,*
2384 *we do encourage physicians to treat a hemodynamically significant PDA before*
2385 *randomizing the patient for the study. To make this feasible physicians are strongly*
2386 *encouraged to determine the presence of a hemodynamically significant PDA at day 7*
2387 *of life. This way the patient can, if necessary according to the local protocol, still be*
2388 *treated with 2 courses of indomethacin / ibuprofen before day 14 of life.*

2389 *If there is an indication to treat a hemodynamically significant PDA with*
2390 *indomethacin/ibuprofen after randomization, study medication is **NOT** stopped. Yet,*
2391 *any synchronous use of indomethacin/ibuprofen and study medication or the*
2392 *occurrence of an intestinal perforation recorded in the case record form, will*

2393 automatically result in so-called **Alert Procedure** (see paragraph 9.4. Such an **Alert**
2394 **Procedure**. This will allow for a close and individual monitoring of possible adverse
2395 effects.

2396 9. If the physician considers extubation not an option because of the general condition
2397 of the infant (e.g. NEC with severe hemodynamic instability and severe abdominal
2398 distension) inclusion in the study can be postponed until the maximum of 14 days
2399 PNA.

2400

2401 **4.4 Sample size calculation**The primary outcome parameter is BPD free survival at 36 weeks
2402 PMA. The a priori risk of death or BPD in preterm infants less than 30 weeks gestation and
2403 ventilated in the second week of life is estimated at 60 – 70%. The meta-analysis on
2404 moderately early dexamethasone treatment estimated an absolute risk reduction (ARR) of
2405 25% (NNT=4) compared with placebo.²⁴ However, there are no data currently available on
2406 the efficacy of hydrocortisone and the suggested cumulative dose in the present study is
2407 considerably lower compared to previously used dexamethasone doses. Since the shown
2408 efficacy of dexamethasone is dependent on the used doses in these trials²⁶, we would
2409 propose a more conservative approach, defining an ARR of 15% or more (NNT=7) as clinically
2410 relevant. With an estimated *a priori* risk for death or BPD at 36 weeks PMA of 60%, a type I
2411 error of 5% (2 tailed) and a power of 80% the number of patients to be included in each
2412 treatment arm would be 175 (total 350). Anticipating a 10% drop out of randomized
2413 patients, 200 patients need to be included in each treatment arm (total 400). Based on a
2414 retrospective analysis of ventilated preterm infants at day 7 of life in the majority of Dutch
2415 NICUs we expect a total of 200 eligible patients each year. With an estimated inclusion rate
2416 of 66% of eligible patients and an inclusion period of 3 years, a total of 400 patients should

2417 be included in the study. For sample size calculation we used Nquery (Statistical Solutions
2418 Ltd., Cork, Ireland).

2419

2420 **5. TREATMENT OF SUBJECTS**

2421 **5.1. Therapeutic details**

2422 5.1.1 Preparation of the trial medication: The infants of the hydrocortisone group will receive
2423 hemisuccinate hydrocortisone 5mg/kg/day Q.I.D for 7 days, followed by 3.75 mg/kg/day
2424 T.I.D. for 5 days, subsequently lowering the frequency by one dose every 5 day. This leads to
2425 a total duration of therapy of 22 days and a cumulative dose of 72.5 mg/kg hydrocortisone
2426 (see appendix 1). The infants in the control group receive saline placebo for the entire 22-day
2427 period in the same frequency as the hydrocortisone group. Both saline and hydrocortisone
2428 schedules will be calculated according to weight on the day of randomisation and not adjusted
2429 to the actual weight during the tapering schedule.

2430

2431 5.1.2 Adjusting study medication for transient short-term adverse effects: previous studies on
2432 *corticosteroids use in the second week of life (mainly dexamethasone) have reported that the*
2433 *following transient short term side-effects: hyperglycaemia, increased risk of infection, and*
2434 *hypertension. Hyperglycaemia and infection occur frequently at the NICU as co-morbidity of*
2435 *preterm birth and its treatment. There is extensive experience in treating these morbidities*
2436 *with, respectively, insulin and antibiotics. Although the incidence of hyperglycaemia and/or*
2437 *infection will be closely monitored (secondary endpoints), in case of an event, the study*
2438 *medication should **NOT** be adjusted.*

2439 *Hypertension is a much less common morbidity after preterm delivery and antihypertensive*
2440 *drugs are not routinely used in neonatal care. Corticosteroids induced hypertension is usually*
2441 *treated and resolved by reducing the dose. So, in case of hypertension, the study medication is*

2442 lowered according to appendix 1 if no other treatable cause of hypertension can be identified.
2443 Hypertension is defined as a **systolic** blood pressure > 80 mmHg for infants 24-26 wks, > 90
2444 mmHg for infants 26-28 wks, and > 100 mmHg for infants \geq 28 wks. Data on the time, reason
2445 and dose adjustment will be collected. The presence of hypertension leading to adjustment of
2446 study medication will be reported via the **Alert Procedure** (see paragraph 9.4).

2447

2448 5.1.3 Stop criteria during study protocol medication (treatment failure): In general,
2449 the use of open label hydrocortisone during the 22 day treatment course is strongly
2450 discouraged. Open label hydrocortisone use **may be considered** in the following conditions:

2451 1. The pulmonary condition is progressively deteriorating and the respiratory index
2452 (MAwP x FiO₂) is >10 for more than 6 consecutive hours.

2453 2. The pulmonary condition of the patient is stable (RI < 10) but not improving over
2454 time. In these circumstances open label hydrocortisone **may be considered** if the
2455 following conditions are met:

2456 a. Extubation was attempted (extubation trial) within 24 hours before
2457 considering open label treatment and this attempt failed.

2458 b. The patient is on study medication for **at least** 10 days (but preferably at a
2459 later time).

2460 The open label hydrocortisone dosage schedule is similar to that used in the study. At that
2461 point in time the study medication is stopped and the patient will be recorded as “treatment
2462 failure”. In case of treatment failure the following data will be collected: timing of treatment
2463 failure, ventilator support and settings, type of open label medication, starting date,
2464 cumulative dose and duration of rescue therapy. The patients will be followed as all other
2465 patients until the clinical endpoints occur or until end of follow up.

2466 ***The use of open label hydrocortisone will be reported via the Alert Procedure (see***
2467 *paragraph 9.4).*

2468

2469 5.1.4 Late rescue therapy outside study protocol (late rescue glucocorticoids): Patients still on
2470 mechanical ventilation after completion of the study medication, i.e. day 22, may be treated
2471 with open label hydrocortisone. *In such cases the physician should first attempt extubation*
2472 *before considering open label use. The open label hydrocortisone dosage schedule is similar*
2473 *to that used in the study (see appendix 1). Data on the starting date, cumulative dose and*
2474 *duration of rescue therapy are collected.*

2475

2476 5.1.5 Anti-hypotensive therapy: In case of persistent hypotension, not (sufficiently)
2477 responding to first line treatment with intravascular volume expansion and inotropes
2478 (dopamine and/or dobutamine) *the use of hydrocortisone is allowed in a dose of 3 mg/kg/day*
2479 *for 5 days. Treatment for hypotension will not be considered as treatment failure. Data on*
2480 *timing, dose and duration will be collected.*

2481

2482 5.1.6 Inhalation corticosteroids: *There is currently insufficient evidence that inhaled*
2483 *corticosteroids will reduce the risk of death or BPD in preterm infants. Use of inhaled*
2484 *corticosteroids in the first weeks of life is therefore strongly discouraged. However, its use is*
2485 *not an exclusion criterion. Data on timing, dose and duration will be collected.*

2486

2487 **5.2. Use of co-intervention**

2488 All randomized patients will be treated according to the guidelines of the individual NICUs.
2489 All participating NICUs explore treatable causes of ventilator dependency during the first
2490 week of life, such as patent ductus arteriosus, sepsis and pneumonia as much as possible and

2491 treat these according to the department protocol. Although all of these conditions can be an
2492 alternative cause of respiratory failure, they are known risk factors for developing BPD and
2493 therefore are not considered exclusion criteria.

2494

2495 This trial will monitor the prognostic important co-interventions and conditions, as described
2496 in section 8.2.

2497

2498 **6. INVESTIGATIONAL MEDICINAL PRODUCT**

2499 **6.1 Name and description of investigational medicinal product**

2500 *In this multicenter study the investigational medicinal product is hydrocortisone. A detailed*
2501 *description of hydrocortisone can be found in the summary of product characteristics (SPC)*
2502 *which is added to this protocol as a separate document.*

2503

2504 **6.2 Summary of findings from non-clinical studies**

2505 *More details on both hydrocortisone and the placebo used in this study can be found in,*
2506 *respectively, the summary of product characteristics (SPC) and investigational medicinal*
2507 *product dossier (IMPD) both added to this protocol as separate documents. In addition to this*
2508 *information, animal studies have shown that hydrocortisone, in contrast to dexamethasone,*
2509 *did not increase the risk of adverse effects on the brain when compared to a placebo.³⁵*

2510

2511 **6.3 Summary of findings from clinical studies**

2512 *Hydrocortisone has several authorized indications as listed in the SPC on page 1. In preterm*
2513 *infants, hydrocortisone is used for the following indications: 1) primary or secondary*
2514 *deficiency of corticosteroids; 2) treatment of hypotension; and 3) anti-inflammatory drug in*

2515 *developing bronchopulmonary dysplasia (BPD). According to the SPC (page 1) only the first*
2516 *indication is authorized. The fact that hydrocortisone is used for other unauthorized*
2517 *indications is not exceptional, because off-label use of medication is more the rule than the*
2518 *exception in neonatology. In this study, hydrocortisone is used for its anti-inflammatory*
2519 *properties on the lungs of preterm infants at high risk for BPD ventilated in the second week*
2520 *of life, aiming to reduce the incidence of BPD. To date, six RCTs investigating a low*
2521 *hydrocortisone dose started within < 72 hours after birth (early treatment) failed to show a*
2522 *clear reduction in the incidence of BPD.³⁷⁻⁴² Only one of these trials reported long-term*
2523 *follow-up, showing no differences in adverse neurodevelopmental sequelae.⁴³ Use of*
2524 *hydrocortisone after the first week of life with a higher dose has been the standard of care in*
2525 *4 of the 10 Dutch NICUs. The University Medical Center Utrecht has used hydrocortisone in*
2526 *an identical treatment schedule as this study for several decades. Several historical cohort*
2527 *studies have shown that hydrocortisone use for this indication (reduction of BPD) did not*
2528 *increase the risk of adverse neurodevelopmental outcome.⁴⁴⁻⁴⁶*

2529

2530 **6.4 Summary of known and potential risks and benefits**

2531 *As studies with hydrocortisone are limited, the assessment of risks and benefits are based on*
2532 *data obtained from previous RCTs investigating other corticosteroids (mainly*
2533 *dexamethasone) in ventilated preterm infants at risk for BPD. Based on these studies,*
2534 *hydrocortisone may facilitate extubation and thereby reduce the total duration of*
2535 *mechanical ventilation. In addition, hydrocortisone may reduce the incidence of BPD. Both*
2536 *these beneficial effects may improve neurodevelopmental outcome. On the other hand, use*
2537 *of hydrocortisone may increase the risk for hyperglycaemia, hypertension, systemic infection,*
2538 *gastrointestinal perforation and a delay in neurodevelopment. However, gastrointestinal*

2539 *perforation and delayed neurodevelopment have only been reported in studies administering*
2540 *corticosteroids in the first week of life and/or during combinations with other medication. In*
2541 *this study the risk of gastrointestinal perforation and delayed neurodevelopment may be*
2542 *reduced because hydrocortisone will be administered after the first week of life and*
2543 *combinations with other drugs will be avoided as much as possible. Infants assigned to the*
2544 *placebo group will not benefit from the aforementioned possible beneficial effects nor be*
2545 *subjected to the possible adverse effect of hydrocortisone.*

2546

2547 **6.5 Description and justification of route of administration and dosage**

2548 *The optimal dose of hydrocortisone is currently unknown. However, the NICU in Utrecht has*
2549 *been using a fixed hydrocortisone treatment regimen for several decades now and this*
2550 *regimen has also been adopted by the other Dutch NICUs using hydrocortisone. Retrospective*
2551 *studies strongly suggest that this is a safe dose, because it was not associated with an*
2552 *increased risk of adverse neurological outcome.^{45,48} Comparing hydrocortisone treated*
2553 *patients with dexamethasone treated patients in other NICUs showed no difference in the*
2554 *incidence of BPD, suggesting that this dose is equally effective in reducing BPD.⁴⁸ Based on*
2555 *these findings and current clinical practice, we decided to adopt the dosing regimen from*
2556 *Utrecht for this study. More details on the dose regimen and the route of administration can*
2557 *be found in paragraph 5.1.*

2558

2559 **6.6 Preparation and labelling of Investigational Medicinal Product**

2560 *Preparation and labelling will be done according to relevant GMP guidelines. Hydrocortisone*
2561 *(Pharmachemie BV Holland) will be provided via the AMC pharmacy (Dr. M. Kemper) and the*
2562 *placebo will be manufactured by ACE Pharmaceuticals BV (Zeewolde, the Netherlands). The*

2563 *SPC of hydrocortisone and the IMPD of the placebo are provided as separate documents. In*
2564 *addition, we have added an example of labels for the vials and boxes as separate documents.*

2565

2566 **6.7 Drug accountability**

2567 *Drug accountability will be according to current GMP guidelines. The “kenniscentrum*
2568 *geneesmiddelen onderzoek” of the AMC pharmacy will take full responsibility and supervision*
2569 *of the drug accountability process.*

2570

2571 **7. METHODS**

2572 **7.1 Randomisation, blinding and treatment allocation**

2573 Written informed consent has to be obtained from either parents or care-givers prior to
2574 randomisation. In case of ventilator dependency after day 7 of life with a suspected diagnosis
2575 of developing BPD, parents receive the study information as soon as possible allowing them
2576 sufficient time to consider participation. The actual decision to include the patient in the trial
2577 should be made between day 7 and 14 PNA. *Following inclusion and randomization, the first*
2578 *dose of study medication should be administered within 24 hours.* Randomization will be
2579 centrally controlled and web-based using a computer program designed for this study. This
2580 trial will be protected from selection bias by using concealed, stratified and blocked
2581 randomisation.

2582

2583 Randomisation will be per center and stratified according to gestational age stratum (Stratum
2584 A: < 27 weeks; Stratum B: \geq 27 weeks), in order to achieve an equal distribution in both
2585 treatment arms. The allocation ratio will be 1:1 with block randomisation using variable block
2586 sizes. Multiple birth infants will be randomised independently, unless the parents or

2587 caretakers explicitly demand that the siblings should be treated according to the same
2588 treatment arm. An automated mechanism to perform twin randomisation is in place.
2589 The infants' parents and all members of the medical team, including investigators, remain
2590 blinded to group assignment throughout the study.

2591

2592 Patient characteristics, including gestational age, birth weight and respiratory status, will be
2593 collected from all eligible infants that are not included in the study. In addition, we will
2594 collect data on why the patients were not included. With this information we will assess
2595 possible bias in patient inclusion.

2596 **7.2 Withdrawal of individual subjects**

2597 Parents or caregivers can leave the study at any time for any reason if they wish to do so
2598 without any consequences.

2599 Note: patients who are considered to have "treatment failure" based on the prespecified
2600 criteria (paragraph 5.1.3) are **NOT** withdrawn from the study, and remain in follow up.

2601

2602 **7.3 Replacement of individual subjects after withdrawal**

2603 The number of withdrawn patients not marked as prespecified treatment failure (see section
2604 7.2) will be replaced.

2605

2606 **7.4 Follow-up of subjects withdrawn from treatment**

2607 Subjects withdrawn from the study will be treated according to the standard of care, including
2608 neurodevelopmental outcome assessment at the outpatient clinic.

2609

2610 **7.5 Premature termination of the trial**

2611 An independent *Data Monitoring Committee (DMC)* will monitor the study on safety aspects
2612 (see section 9.4) and if necessary recommend termination of the study.

2613

2614 **7.6 Breaking the randomization code**

2615 *Unblinding is only performed in emergency situations where knowledge of the identity of the*
2616 *study drug is considered absolutely necessary for the clinical management of the subject. If*
2617 *local investigator or attending physician decides unblinding is essential, (s)he will make*
2618 *every effort to contact the PI before unblinding to discuss options. For this purpose a 24/7*
2619 *reachable telephone service will be installed. Details of the unblinding procedure will be*
2620 *defined in the study specific working instructions.*

2621 **7.7. Endpoints**

2622 7.7.1. Primary endpoint: the dichotomous variable *BPD free survival at 36 weeks PMA*. BPD
2623 at 36 weeks PMA will be assessed according to the NIHCHD Consensus Statement defining
2624 normal oxygen saturation as 86%-94%. The severity of the BPD will be assessed as proposed
2625 by Jobe et.al.²¹, since the severity of BPD has a high association with neurodevelopmental
2626 sequelae.¹² In case of supplemental oxygen delivery >21% and < 30% or low flow at 36 weeks
2627 PMA, the oxygen reduction test as described by Walsh et.al.^{21,49,50} should be performed. A
2628 positive oxygen reduction test has a high correlation with the risk on discharge home with
2629 oxygen, the length of hospital stay, and pulmonary morbidity requiring hospital readmission
2630 during the first year of life. For practical guidance on the use of the oxygen reduction test
2631 please go to appendix 2.

2632

2633 7.7.2. Secondary endpoints:

- 2634 • treatment failure as defined in section 5.1.3

- 2635 • mortality at 28 days PNA, 36 weeks PMA and at hospital discharge
- 2636 • BPD at 28 days
- 2637 • failure to extubate 3, 7, 14 and 21 days after initiating therapy
- 2638 • duration of mechanical ventilation
- 2639 • use of “rescue treatment” with hydrocortisone outside the study protocol
- 2640 • total time on supplemental oxygen
- 2641 • length of hospital stay
- 2642 • incidence of hypertension, as defined in paragraph 5.1.2
- 2643 • hyperglycaemia requiring the use of insulin therapy
- 2644 • nosocomial infection, like sepsis, meningitis and pneumonia
- 2645 • pulmonary hemorrhage, pneumothorax and pulmonary interstitial emphysema
- 2646 • hemodynamic significant patent ductus arteriosus for which medical intervention or
- 2647 surgical ligation is needed
- 2648 • necrotising enterocolitis (NEC), diagnosed at surgery, autopsy or by radiographic
- 2649 finding of pneumatosis intestinalis or hepatobiliary gas (Bell stage II)
- 2650 • gastrointestinal bleeding
- 2651 • isolated gastrointestinal perforation diagnosed on abdominal radiography
- 2652 • intraventricular haemorrhage (IVH) and/or periventricular leucomalacia (PVL),
- 2653 including grading on cerebral ultrasonography according to protocol defined by Ment
- 2654 et.al.⁵¹
- 2655 • retinopathy of prematurity, including grading following international classification⁵²
- 2656 • weight, head circumference and length at 36 weeks PMA
- 2657 • long-term health and neurodevelopmental sequelae, assessed at 2 years c.a.:

- 2658 ○ readmissions since first discharge home
- 2659 ○ weight, length and head circumference at 24 months c.a.
- 2660 ○ Bayley Scales of Infant Development III, Mental Developmental Index and
- 2661 Psychomotor Developmental Index
- 2662 ○ cerebral palsy and severity of cerebral palsy using gross motor function
- 2663 classification system
- 2664 ○ hearing loss requiring hearing aids
- 2665 ○ blindness
- 2666 ○ behavioural problems (child behaviour checklist)

2667

2668 All primary and secondary endpoints are measured as part of standard usual care in the
2669 Netherlands and Belgium, and will be derived from the charts of the patients by the
2670 investigators.

2671

2672 **8. DATA COLLECTION AND STATISTICAL ANALYSIS**

2673 **8.1 Baseline characteristics**

2674 Baseline characteristics are collected prior to inclusion and randomization with respect to the
2675 following baseline characteristics: demographic details and patient characteristics, such as
2676 gestational age, small for gestational age, antenatal problems, antenatal steroids, surfactant
2677 therapy, mode of delivery, resuscitation details, Apgar scores, presence of IVH/PVL, and
2678 occurrence of PDA. Base line characteristics on ventilator settings, gas exchange will be
2679 collected on day of randomization.

2680

2681 **8.2 Co-interventions**

2682 *Apart from the study medication all patients will receive standard care, including co-*
2683 *medication such as surfactant, inhaled nitric oxide. methylxanthines, vitamin A, antibiotics,*
2684 *antimycotic therapy, diuretics, ibuprofen/indomethacine, inotropes, and inhaled*
2685 *corticosteroids. These co-medications are prescribed on the basis of (inter)national*
2686 *guidelines and/or local protocols. Since the route of administration (e.g. oral or IV), the dose*
2687 *and frequency may vary continuously depending on the weight and the clinical condition of*
2688 *the patients, only name, start and stop date are recorded in the CRF. For all other drugs used*
2689 *during the admission data will be recorded according to GCP guidelines.*
2690 *Also the ventilation mode with the ventilator settings will be recorded and analyzed.*

2691

2692 **8.3 Statistical analysis**

2693 Normally distributed data will be presented as mean \pm standard deviations, not-normally
2694 distributed data as medians and (interquartile) ranges. Categorical data will be analysed
2695 using the Chi-square test. Continuous data will be analysed using the Student's *t* test or
2696 Mann-Whitney test as appropriate. Both intention-to-treat and per-protocol analysis will be
2697 employed. The effect of hydrocortisone on the primary outcome death or BPD will be
2698 assessed by multi-variable logistic regression analysis including possible confounders.
2699 Statistical significance is set at $p < 0.05$.

2700

2701 **9. SAFETY REPORTING**

2702 **9.1 Section 10 WMO (Wet Medisch-wetenschappelijk Onderzoek met Mensen)**

2703 In accordance with section 10, subsection 1, of the Dutch WMO, the investigator will inform
2704 the subjects' parents or caregivers and the reviewing accredited METC (*Medisch Ethische*
2705 *Toetsingscommissie*) if anything occurs, on the basis of which it appears that the
2706 disadvantages of participation may be significantly greater than was foreseen in the research

2707 proposal. The study will be suspended pending further review by the accredited METC,
2708 except insofar as suspension would jeopardise the subjects' health. The investigator will
2709 ensure that all subjects' parents or caregivers are kept informed.

2710

2711 **9.2 Adverse and serious adverse events (SAE)**

2712 Adverse events are defined as any undesirable experience occurring to a subject during a
2713 clinical trial, whether or not considered related to the investigational drug. All adverse
2714 events observed by the investigator or his staff will be recorded. A **serious adverse event** is
2715 any untoward medical occurrence or effect that at any dose

2716 - results in death;

2717 - is life threatening (at the time of the event);

2718 - requires hospitalization or prolongation of existing inpatients' hospitalization;

2719 - results in persistent or significant disability or incapacity;

2720 - is a congenital anomaly or birth defect (not applicable in this trial);

2721 - *other important events that may jeopardize the safety of the subject or may require*

2722 *intervention to prevent one of the outcomes listed above.*

2723

2724 *All SAEs will be reported, as described below (9.2.1), by the principle investigator to the Data*

2725 *Monitoring Committee (DMC) and to the accredited METC that approved the protocol,*

2726 *according to the requirements of that METC.*

2727

2728 9.2.1 Context-specific SAE reporting

2729 *This study population (critically ill preterm infants) has a high risk of serious complications*
2730 *(so-called “context-specific SAE’s”), which are inherent to their vulnerable condition and*
2731 *unrelated to the intervention which is under evaluation in this trial.*

2732 *These complications are included in the primary and secondary outcomes of this study and*
2733 *are recorded in the Case Report Form. This documentation will include the date of diagnosis,*
2734 *classification/gradation of the complication, type of action taken if appropriate (with some*
2735 *complications a wait and see approach is warranted). Since these complications are highly*
2736 *interrelated and of longitudinal character, it is impossible to indicate an exact date for the*
2737 *resolution or stabilisation of each specific diagnosis. Therefore, we will use the date of*
2738 *discharge from the NICU for this purpose. As long as the child is admitted to the NICU, the*
2739 *complication will be classified as ongoing.*

2740 *In light of the above, immediate and individual reporting of all these condition related*
2741 *complications will not enhance the safety of study.^{1,2} This is also in accordance with CCMO*
2742 *regulations (<http://www.ccmo-online.nl/main.asp?pid=25&sid=49&ssid=178>)*

2743 *The context-specific SAEs that will be identified include the events listed under paragraph*
2744 *7.7.2, on page 27 and 28 of the protocol.*

2745 *Once a year, an overview of the aforementioned complications for each treatment arm and*
2746 *ordered by organ system will be presented to the DMC and METC. This overview will consist*
2747 *of the following information: name of the complication, date of diagnosis,*
2748 *classification/gradation of the complication, type of action taken, date of discharge or*
2749 *ongoing.^{53,54}*

2750 9.2.2 Suspected unexpected serious adverse reactions (SUSAR)

2751 *Adverse reactions are all untoward and unintended responses to an investigational product*
2752 *related to any dose administered.*

2753

2754 *Unexpected adverse reactions are adverse reactions, of which the nature, or severity, is not*
2755 *consistent with the applicable product information (see SPC/IMPd) or the context-specific*
2756 *SAEs listed in paragraph 9.2.1.*

2757

2758 *Any SUSAR should be reported, as soon as it occurs, to the principle investigator and the*
2759 *study coordinator via the study website (**Alert Procedure**, see paragraph 9.4). The PI will*
2760 *report expedited all SUSARs through the web portal ToetsingOnline to the METC, competent*
2761 *authority, Medicine Evaluation Board as well as to the competent authorities in other*
2762 *Member States, according to the requirements of the Member States.*
2763 *The expedited reporting will occur not later than 15 days after the PI has first knowledge of*
2764 *the adverse reactions. For fatal or life threatening cases the term will be maximal 7 days for*
2765 *a preliminary report with another 8 days for completion of the report.*

2766

2767 9.2.3 Annual safety report

2768 *In addition to the expedited reporting of SUSARs, the PI will submit, once a year throughout*
2769 *the clinical trial, a safety report to the DMC, accredited METC, competent authority, Medicine*
2770 *Evaluation Board and competent authorities of the concerned Member States as well as the*
2771 *investigators of all participating centers.*

2772 *This safety report consists of:*

- 2773 – *a list of all suspected (unexpected or expected) serious adverse reactions, along with an*
2774 *aggregated summary table of all reported serious adverse reactions*
- 2775 – *a report concerning the safety of the subjects, consisting of a complete safety analysis and*
2776 *an evaluation of the balance between the efficacy and the harmfulness of the medicine*
2777 *under investigation.*

2778

2779 **9.3 Follow-up of adverse events**

- 2780 *All adverse events will be followed until they have abated, or until a stable situation has been*
2781 *reached. Depending on the event, follow up may require additional tests or medical*
2782 *procedures as indicated. According to the standard of care, all infants will participate in the*
2783 *usual NICU follow-up program. This program is targeted at evaluating and coordinating*
2784 *diagnostic procedures and treatment of all prematurity related problems, in close*
2785 *cooperation with regional and local pediatricians.*

2786

2787 **9.4 Data Monitoring Committee (DMC), the Alert Procedure**

- 2788 *An external Data Monitoring Committee (DMC) will monitor efficacy and safety outcomes*
2789 *and will provide the trial's Steering Committee with recommendations regarding continuing*
2790 *or stopping the trial (for all patients or subgroups of patients) when approximately 25%*
2791 *(safety only), 50% (safety and efficacy) and 75% (safety and efficacy) of the anticipated*
2792 *outcome data are available. Data summaries for the DMC will be prepared by a statistician*
2793 *who is not a member of the investigating team. The safety data will include, but not be*
2794 *restricted to, serious adverse events and the safety outcomes listed as secondary outcomes.*
2795 *The DMC will be blinded to the treatment allocation. During the closed DMC meetings, the*
2796 *data manager will be stand-by to reveal the allocation labels if the DMC thinks this is*

2797 *necessary. If the DMC recommends modification or cessation of the study protocol, this will*
2798 *be discussed with the Steering Committee, who will make the decision. The DMC will be*
2799 *composed of 3 individuals: a neonatologist with extensive knowledge of BPD, a statistician*
2800 *who has experience with trials, and some experience on previous DMCs and a*
2801 *pharmacologist with extensive knowledge of the use of hydrocortisone (corticosteroids) in*
2802 *neonates. The Steering Committee will propose a detailed mandate and review this with the*
2803 *DMC, from the outset. Identification and circulation of external evidence (e.g., from other*
2804 *trials/systematic reviews) is not the responsibility of the DMC members. It is the*
2805 *responsibility of the PI to provide any such information to the DMC.*

2806

2807 *To enhance the safety of patients in the STOP-BPD trial, a special alert procedure has been*
2808 *added to the CRF and the website (SUSAR), “The Alert Procedure”. This tool is used to*
2809 *monitor special conditions and acute situations that need the direct attention of the principle*
2810 *investigator and the study coordinator. If necessary the Steering Committee can decide to*
2811 *alert the DMC. Furthermore, the Steering Committee will provide a summary report after*
2812 *every 10 alerts to the DMC.*

2813

2814 *There are 5 situations when the **Alert Procedure** must be used:*

- 2815 *1. Any synchronous use of indomethacin/ibuprofen and study medication*
- 2816 *2. Any intestinal perforation occurring during or after the study medication treatment*
2817 *course*
- 2818 *3. Occurrence of hypertension as defined*
- 2819 *4. Any use of open label hydrocortisone*
- 2820 *5. Occurrence of a SUSAR*

2821

2822 *The “Alert Procedure” will run in the background for the first 4 conditions. CRF data will be*
2823 *linked automatically and an email will be send to principal investigator and the study*
2824 *coordinator automatically once conditions 1 to 4 occur. In case of a SUSAR the local*
2825 *investigator can alert the principal investigator and the study coordinator via a SUSAR email*
2826 *button on the trial website.*

2827

2828 **10. ETHICAL CONSIDERATIONS**

2829 **10.1 Regulation statement**

2830 The study will be conducted according to the principles of the Declaration of Helsinki⁵⁵ and
2831 in accordance with the Medical Research Involving Human Subjects Act (WMO).

2832

2833 **10.2 Recruitment and informed consent**

2834 Patients will be recruited and their parents will be informed and asked for consent by the
2835 attending paediatricians. Informed written consent must be obtained from the parents prior to
2836 randomisation for the study. The patient information letter and informed consent are provided
2837 in section I of the study dossier. The right of a parent or patient to refuse participation without
2838 giving reasons will be respected. The parents will remain free to withdraw their child at any
2839 time from the study without consequences for further treatment.

2840

2841 **10.3 Benefits and risks assessment, group relatedness**

2842 Burden: All infants participating in (either treatment arm of) the study are subjected to
2843 routine neonatal intensive care. The administration of the study intervention itself
2844 (hydrocortisone or placebo administration) does not pose an extra burden on the patients
2845 since intravenous access will be necessary for other clinical reasons. If this is no longer the

2846 case, study medication may be administered via the oral route. This study does not require
2847 extra investigations or interventions.

2848 Benefit and risks: Hydrocortisone may facilitate extubation and thereby reduce the total
2849 duration of mechanical ventilation. In addition, hydrocortisone may reduce the incidence of
2850 BPD. Both these beneficial effects may improve neurodevelopmental outcome. On the other
2851 hand, use of hydrocortisone may increase the risk for (often transient) hyperglycemia,
2852 hypertension and systemic infection. Although the increased risk of gastrointestinal
2853 perforation has up to now only been reported during the early (within the first 96 hours of
2854 life) administration of corticosteroids, the risk may also be increased when administering
2855 hydrocortisone after the first week of life. Finally, early (within the first 96 hours of life) use
2856 of dexamethasone has been associated with an increase risk for neurodevelopmental
2857 sequelae. Historical cohort studies investigating the use of hydrocortisone after the first
2858 week of life have found no evidence to support this. Infants assigned to the placebo group
2859 will not benefit from the aforementioned possible beneficial effects nor be subjected to the
2860 possible adverse effect of hydrocortisone.

2861 Group relatedness: BPD is a complication occurring exclusively in preterm infants. Any
2862 intervention aiming to reduce the risk of this complication therefore needs to be studied in
2863 this specific population at risk.

2864

2865 **10.4 Compensation for injury**

2866 The sponsor/investigator has a liability insurance which is in accordance with article 7,
2867 subsection 6 of the WMO. The sponsor (also) has an insurance which is in accordance with
2868 the legal requirements in the Netherlands (Article 7 WMO and the Measure regarding

2869 Compulsory Insurance for Clinical Research in Humans of 23rd June 2003). This insurance
2870 provides cover for damage to research subjects through injury or death caused by the study.
2871 1. € 450.000,-- (i.e. four hundred and fifty thousand Euro) for death or injury for each
2872 subject who participates in the Research;
2873 2. € 3.500.000,-- (i.e. three million five hundred thousand Euro) for death or injury for all
2874 subjects who participate in the Research;
2875 3. € 5.000.000,-- (i.e. five million Euro) for the total damage incurred by the organization
2876 for all damage disclosed by scientific research for the Sponsor as ‘verrichter’ in the
2877 meaning of said Act in each year of insurance coverage.
2878 The insurance applies to the damage that becomes apparent during the study or within 4 years
2879 after the end of the study.

2880

2881 **10.5 Incentives**

2882 Participants will not receive a financial compensation for participation as an incentive.

2883

2884 **11. ADMINISTRATIVE ASPECTS AND PUBLICATION**

2885 **11.1 Handling and storage of data and documents**

2886 Datamanagement will be implemented according to Good Clinical Practice (GCP)-guidelines.

2887 Patient data will be entered by way of an eCRF in a central GCP proof internet based

2888 database to facilitate on-site data-entry. Security is guaranteed with login names, login

2889 codes and encrypted data transfer. An experienced datamanager will maintain the database

2890 and check the information in the database for completeness, consistency and plausibility.

2891

2892 The data of all subjects will be coded and this coding will not be retraceable to the individual

2893 patient. The key to this coding is safeguarded by the investigator. A limited number of

2894 people have access to the source data. These are the principal investigator, investigating
2895 doctor and investigating personnel. Personal data are only processed by the researchers or
2896 by those who fall directly under their authority. In addition, the study monitor, quality
2897 assurance auditor, employees from the METC and the Health Care Inspectorate of the
2898 Ministry of Health, welfare and Sport (Nederlandse Inspectie voor de Gezondheidszorg) have
2899 access to the source data. All are subject to the pledge of confidentiality. Data and human
2900 material will be stored for 15 years strictly confidential.

2901

2902 **11.2 Amendments**

2903 Amendments are changes made to the trial after a favourable opinion by the accredited METC
2904 has been given. All amendments will be notified to the METC that gave a favourable opinion.
2905 All substantial amendments will be notified to the METC and to the competent authority.
2906 Non-substantial amendments will not be notified to the accredited METC and the competent
2907 authority, but will be recorded and filed by the Steering Committee.

2908

2909 **11.3 Annual progress report**

2910 If requested, an annual progress report of the progress of the trial will be provided to the
2911 accredited METC. Information will be provided on the date of inclusion of the first subject,
2912 numbers of subjects included and numbers of subjects that have completed the trial, serious
2913 adverse events/ serious adverse reactions, other problems, and amendments. In case the study
2914 is ended prematurely, the investigator will notify the accredited METC, including the reasons
2915 for the premature termination. Within one year after the end of the study, the
2916 investigator/sponsor will submit a final study report with the results of the study, including
2917 any publications/abstracts of the study, to the accredited METC.

2918

2919 **11.4 Public disclosure and publication policy**

2920 The study will be registered in the EUDRACT, the website of the Dutch National Competent
2921 Authority, the 'Centrale Commissie Mensgebonden Onderzoek' (CCMO), Dutch public trial
2922 registry, part of the WHO registry. The results of the study will be published in peer-
2923 reviewed international medical journals. In addition, the results of the study will be used for
2924 development and implementation of a guideline on treatment of BPD, which will benefit
2925 future patients.

2926

2927 **12. ORGANISATION**

2928 **12.1 Steering Committee**

2929 The Steering Committee is the main policy and decision making committee of the study and
2930 has final responsibility for the scientific conduct of the study. It will be composed of
2931 representatives of the sponsor, of the investigators of the participating centres and of the
2932 MCRN. The specific tasks of the Steering Committee are:

- 2933
- 2934 • Approve the study protocol
 - 2935 • Approve necessary changes in the protocol based on considerations of feasibility
 - 2936 • Act upon recommendations of the Data Monitoring Committee
 - 2937 • Review performance reports of the study sites
 - 2938 • Resolve operational problems brought before it by the project manager
 - 2939 • Approve study reports and papers for publication.

2939

2940 **12.2 Data Monitoring Committee**

2941 An independent Data Monitoring Committee (DMC) will be created specifically for this trial.

2942 The DMC will act in advisory capacity to the Steering Committee. See Paragraph 9.4 for a

2943 description of the membership, tasks and responsibilities of the DMC.

2944

2945 **12.3 Clinical Project Manager / Central Study Coordinator**

2946 An experienced clinical project manager (CPM) from MCRN will manage the quality of the

2947 study according to the Good Clinical Practice (GCP)-guidelines, supervise the data monitoring

2948 process, and verify the quality of conduct of all study personnel. The CPM and/or clinical

2949 research associate (CRA) will arrange that the study personnel is adequately trained in GCP

2950 and study protocol, where needed. The CPM meets regularly with the CRA, data managers,

2951 the Data Safety Monitoring Committee (DSMC), financial departments of study centers, and

2952 all other relevant parties to assure study progress, quality and financials are according to

2953 planning. The CPM will coordinate regulatory authority and ethics committee submissions.

2954 The CPM provides regularly an overall study status report to the Steering Committee

2955

2956 **12.4 Study Monitoring**

2957 The study will be monitored by an experienced monitor from MCRN throughout its duration

2958 by means of personal visits to the Investigator's facilities and through other communications

2959 (e.g., telephone calls, written correspondence).

2960 Monitoring visits will be scheduled at mutually agreeable times periodically throughout the

2961 study and at frequency deemed appropriate for the study.

2962 These visits will be conducted to evaluate the progress of the study, ensure the rights and

2963 wellbeing of the subjects are protected, check that the reported clinical study data are

2964 accurate, complete and verifiable from source documents, and the conduct of the study is in

2965 compliance with the approved protocol and amendments, GCP and applicable national
2966 regulatory requirements. A monitoring visit will include a review of the essential clinical
2967 study documents (regulatory documents, CRFs, source documents, drug disposition records,
2968 subject informed consent forms, etc.) as well as discussion on the conduct of the study with
2969 the Investigator and staff. The Investigator and staff should be available during these visits to
2970 facilitate the review of the clinical study records and resolve/document any discrepancies
2971 found during the visit.

2972

2973 **12.5 Quality Assurance Audits and Inspections**

2974 The Sponsor's (or an authorized representative's) Quality Assurance department may conduct
2975 audits of all aspects of the clinical study either during the study or after the study has been
2976 completed. By participating this trial the investigator agrees to this requirement.

2977 The clinical study may also be subject to inspection by regulatory authorities as well as the
2978 accredited Medical Ethical Committee/ Competent authority to ascertain that the study is
2979 being or has been conducted in accordance with protocol requirements, GCP, as well as the
2980 applicable regulatory requirements.

2981

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2986 **13. REFERENCES**

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APPENDIX 1 STUDIE MEDICATIE SCHEMA

3144

| Step 1: Fill in patient data in yellow cubicles. Use weight at day of randomization. | | Step 2: Fill in date and time of first administration study medication in green cubicle. Format for filling date/time: dd-mm-yyyy hr:mm | | Step 3: In case of hypertension related to study medication, fill in the red cubicle. The program will automatically skip the next dose and commence the following dose with a lower daily frequency. | | Step 4: For print out of study medication list, press: <input type="button" value="Print"/> | | | | | | | |
|--|---------------|---|----------|---|----------------|---|----------------|----------|---------------|--------------|---------------|----------|--------------|
| Study identification | | First administration | | | |  | | | | | | | |
| Name | | Date/time | | | | | | | | | | | |
| Date of birth | | Lowering dosage regimen | | | | | | | | | | | |
| Weight | | Date/time | | | | | | | | | | | |
| gram | | | | | | | | | | | | | |
| Day in regimen | Time | Times per day | mg/dose | Daily dose/kg | Day in regimen | Time | Times per day | mg/dose | Daily dose/kg | | | | |
| Day 1 | 0-01-00 0:00 | 4 x | 0.00 mg. | 5 mg/kg/d | Day 8 | 7-01-00 0:00 | 3 x | 0.00 mg. | 3.75 mg/kg/d | | | | |
| | 0-01-00 6:00 | | | | | 7-01-00 8:00 | | | | | | | |
| | 0-01-00 12:00 | | | | | 7-01-00 16:00 | | | | | | | |
| | 0-01-00 18:00 | | | | | Day 9 | | | | 8-01-00 0:00 | 3 x | 0.00 mg. | 3.75 mg/kg/d |
| Day 2 | 1-01-00 0:00 | 4 x | 0.00 mg. | 5 mg/kg/d | 8-01-00 8:00 | | | | | | | | |
| | 1-01-00 6:00 | | | | 8-01-00 16:00 | | | | | | | | |
| | 1-01-00 12:00 | | | | Day 10 | | 9-01-00 0:00 | 3 x | 0.00 mg. | 3.75 mg/kg/d | | | |
| | 1-01-00 18:00 | | | | | 9-01-00 8:00 | | | | | | | |
| Day 3 | 2-01-00 0:00 | 4 x | 0.00 mg. | 5 mg/kg/d | | 9-01-00 16:00 | | | | | | | |
| | 2-01-00 6:00 | | | | | Day 11 | 10-01-00 0:00 | | | | 3 x | 0.00 mg. | 3.75 mg/kg/d |
| | 2-01-00 12:00 | | | | 10-01-00 8:00 | | | | | | | | |
| | 2-01-00 18:00 | | | | 10-01-00 16:00 | | | | | | | | |
| Day 4 | 3-01-00 0:00 | 4 x | 0.00 mg. | 5 mg/kg/d | Day 12 | | 11-01-00 0:00 | 3 x | 0.00 mg. | 3.75 mg/kg/d | | | |
| | 3-01-00 6:00 | | | | | 11-01-00 8:00 | | | | | | | |
| | 3-01-00 12:00 | | | | | 11-01-00 16:00 | | | | | | | |
| | 3-01-00 18:00 | | | | | Day 13 | 12-01-00 0:00 | | | | 2 x | 0.00 mg. | 2.5 mg/kg/d |
| Day 5 | 4-01-00 0:00 | 4 x | 0.00 mg. | 5 mg/kg/d | 12-01-00 12:00 | | | | | | | | |
| | 4-01-00 6:00 | | | | Day 14 | | 13-01-00 0:00 | 2 x | 0.00 mg. | 2.5 mg/kg/d | | | |
| | 4-01-00 12:00 | | | | | | 13-01-00 12:00 | | | | | | |
| | 4-01-00 18:00 | | | | | Day 15 | 14-01-00 0:00 | | | | 2 x | 0.00 mg. | 2.5 mg/kg/d |
| Day 6 | 5-01-00 0:00 | 4 x | 0.00 mg. | 5 mg/kg/d | | | 14-01-00 12:00 | | | | | | |
| | 5-01-00 6:00 | | | | Day 16 | | 15-01-00 0:00 | 2 x | 0.00 mg. | 2.5 mg/kg/d | | | |
| | 5-01-00 12:00 | | | | | | 15-01-00 12:00 | | | | | | |
| | 5-01-00 18:00 | | | | | Day 17 | 16-01-00 0:00 | | | | 2 x | 0.00 mg. | 2.5 mg/kg/d |
| Day 7 | 6-01-00 0:00 | 4 x | 0.00 mg. | 5 mg/kg/d | | | 16-01-00 12:00 | | | | | | |
| | 6-01-00 6:00 | | | | Day 18 | | 17-01-00 0:00 | 1 x | 0.00 mg. | 1.25 mg/kg/d | | | |
| | 6-01-00 12:00 | | | | | | 18-01-00 0:00 | | | | | | |
| | 6-01-00 18:00 | | | | | Day 19 | 19-01-00 0:00 | | | | 1 x | 0.00 mg. | 1.25 mg/kg/d |
| Day 8 | 7-01-00 0:00 | 4 x | 0.00 mg. | 5 mg/kg/d | | | 20-01-00 0:00 | | | | | | |
| | 7-01-00 6:00 | | | | Day 20 | | 21-01-00 0:00 | 1 x | 0.00 mg. | 1.25 mg/kg/d | | | |
| | 7-01-00 12:00 | | | | | | Day 21 | | | | | | |
| | 7-01-00 18:00 | | | | | Day 22 | | | | | 23-01-00 0:00 | 1 x | 0.00 mg. |

3145

3146 **APPENDIX 2**

3147

3148 **Oxygen reduction test**

3149 Bronchopulmonary dysplasia (BPD) can be classified in to mild, moderate or severe
3150 depending on the amount and duration of supplemental oxygen and the level of respiratory
3151 support. If a patient has received supplemental oxygen for more than 28 d ($FiO_2 > 0.21$ for
3152 more than 12 hours each day) and is receiving no extra oxygen at 36 weeks postmenstrual
3153 age (PMA), he or she is classified as having mild BPD. If the oxygen need at 36 weeks PMA is
3154 between 0.21 and 0.30, BPD is classified as moderate and in case of a $FiO_2 > 0.30$ and/or
3155 receiving continuous positive airway pressure (nCPAP)/mechanical ventilation as severe.

3156 It is important to realize that the duration of supplemental oxygen is highly dependent on
3157 target ranges of transcutaneous oxygen saturation (SpO_2) and the alertness of the clinician
3158 to actively wean oxygen delivery.

3159 To make sure that patients receive supplemental oxygen for pulmonary reasons and to
3160 standardize the amount of oxygen to predefined and uniform SpO_2 targets, Walsh et al.
3161 developed a so-called oxygen reduction test at 36 weeks PMA. Patients are eligible for
3162 testing if they need a FiO_2 between 0.21 and 0.30 to maintain the SpO_2 between 90-96% **or** if
3163 they receive a $FiO_2 > 0.30$ resulting in a $SpO_2 > 96\%$. Patients supported with nasal cannulae
3164 (flow not nCPAP) without supplemental oxygen, and patients treated with
3165 nCPAP/mechanical ventilation or with a $FiO_2 > 0.30$ resulting in a $SpO_2 < 96\%$ do not need
3166 additional testing, and are, respectively, classified as having mild and severe BPD.

3167 ***The oxygen reduction test***3168 **Indications:**

3169 - $\text{FiO}_2 > 0.21$ and < 0.30 with oxygen saturation ranges between 90% and 96%

3170 - $\text{FiO}_2 > 0.30$ with a oxygen saturation range above 96%

3171 Methods:

3172 The patient is placed in supine position and the test is initiated 30 minutes after a feeding. The

3173 supplemental oxygen requirement will be gradually weaned to room air while monitoring

3174 SpO_2 . The diagnosis moderate BPD can be rejected when the SpO_2 remain above $\geq 88\%$ in

3175 room air during 1 hour without apnea or bradycardia.

3176 The diagnosis moderate BPD is confirmed if the saturation goes below 80% during > 1 minute

3177 or remains between 80-87% during > 5 minutes. All occurrences of movement artifact

3178 (defined as visible motion of the infant together with loss of plethysmograph signal from the

3179 monitor) are recorded and corresponding saturation values are to be deleted.

3180

3181 The test contains 4 phases

3182 Phase 1: Baseline evaluation

3183 For 15 minutes heart rate, respiratory rate, SpO_2 , number of apnea (cessation of breathing $>$

3184 20 seconds) and bradycardia (heart rate $< 80/\text{min}$ during > 10 sec) will be collected.

3185 Phase 2: Oxygen reduction

3186 The supplemental oxygen will be weaned by 2% to room air, after which the flow will be

3187 weaned with 0.1 L/min to 0 L/min; The nasal cannulae will be removed from the nares, but

3188 not removed from the face.

3189 Phase 3: Observation period

3190 For the period of 1 hour the heart rate, respiratory rate, and SpO_2 in room air will be

3191 registered. In case of a desaturation below 80% for > 1 minute or saturation between 80-87%

3192 for > 5 minutes, the supplemental oxygen will be restarted and the test will be aborted.

3193 *Phase 4: Back to situation before the test*

3194 The level of supplemental oxygen and flow will be reset to the status before the test.

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3241 PROTOCOL

3242 **Systemic Hydrocortisone To Prevent Bronchopulmonary Dysplasia in preterm**3243 **infants: the SToP-BPD study**3244 **A multicenter randomised placebo controlled trial**

| | |
|-------------------------------|---|
| Protocol ID | Systemic Hydrocortisone To Prevent Bronchopulmonary Dysplasia in preterm infants: the SToP-BPD study |
| Short title | Hydrocortisone for bronchopulmonary dysplasia |
| Version | 4 |
| Date | 25 April 2012 |
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3319 **LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS**

3320

| | | |
|------|---------|--|
| 3321 | ARR | Absolute Risk Reduction |
| 3322 | BPD | BronchoPulmonary Dysplasia |
| 3323 | BW | Birth Weight |
| 3324 | CDP | Continuous Distension Pressure |
| 3325 | CGA | Corrected Gestational Age |
| 3326 | CP | Cerebral Palsy |
| 3327 | DNRN | Dutch Neonatal Research Netwerk; in Dutch: Nederlands Neonataal |
| 3328 | | Research Netwerk (NNRN) |
| 3329 | DMC | Data Monitoring & Safety Committee |
| 3330 | ESEMC | External Safety and Efficacy Monitoring Committee |
| 3331 | GA | Gestational Age |
| 3332 | HFO | High Frequency Oscillation |
| 3333 | IMP | Investigational Medicinal Product |
| 3334 | IVH | IntraVentricular Haemorrhage |
| 3335 | MAwP | Mean Airway Pressure |
| 3336 | METC | Medical research ethics committee (MREC); in Dutch: Medisch |
| 3337 | | Ethische Toetsing Commissie |
| 3338 | MRI | Magnetic Resonance Imaging |
| 3339 | NEC | Necrotising EnteroColitis |
| 3340 | NICU | Neonatal Intensive Care Unit |
| 3341 | NICHD | National Institutes for Child Health and Human Development |
| 3342 | NNT | Number Needed to Treat |
| 3343 | NVK | Dutch Society of Pediatricians; in Dutch: Nederlandse Vereniging voor |
| 3344 | | Kindergeneeskunde |
| 3345 | PDA | Persistent Ductus Arteriosus |
| 3346 | PMA | PostMenstrual Age |
| 3347 | PNA | PostNatal Age |
| 3348 | PVL | PeriVentricular Leucomalacia |
| 3349 | RCT | Randomised Controlled Trial |
| 3350 | RI | Respiratory Index |
| 3351 | SAE | Serious Adverse Event |
| 3352 | SD | Standard Deviation |
| 3353 | Sponsor | The sponsor is the party that commissions the organisation of |
| 3354 | | performance of the research, for example a pharmaceutical company, |
| 3355 | | academic hospital, scientific organisation or investigator. A party that |
| 3356 | | provides funding for a study but does not commission it is not |
| 3357 | | regarded as the sponsor, but referred to as a subsidising party. |
| 3358 | VLBW | Very Low Birth Weight |
| 3359 | WMO | Medical Research Involving Human Subjects Act; in Dutch: Wet |
| 3360 | | Medisch-wetenschappelijk Onderzoek met Mensen |
| 3361 | | |

3362

3363 **SUMMARY**

3364 **Background:** Randomised controlled trials (RCTs) have shown that treatment of chronically
3365 ventilated preterm infants after the first week of life with dexamethasone reduces the
3366 incidence of bronchopulmonary dysplasia (BPD). However, there are concerns that its use
3367 may increase the risk of adverse neurodevelopmental outcome. Hydrocortisone has been
3368 suggested as an alternative therapy. So far no RCT has investigated its efficacy when
3369 administered after the first week of life to ventilated preterm infants.

3370 **Objective:** To establish the efficacy of hydrocortisone given after one week of life to reduce
3371 the incidence of the combined outcome death or BPD in chronically ventilated preterm
3372 infants.

3373 **Study design:** Randomised double blind placebo controlled multicenter study.

3374 **Study population:** Very low birth weight infants (GA<30weeks and/or BW<1250grams),
3375 ventilator dependent at a postnatal age of 7 – 14 days.

3376 **Intervention:** Administration of hydrocortisone or placebo during a 22 day tapering
3377 schedule.

3378 **Outcome parameters:** Primary outcome measure is survival free of BPD at 36 weeks
3379 postmenstrual age (PMA). Secondary outcomes are short term effects on the pulmonary
3380 condition, adverse effects during hospitalization, and long-term neurodevelopmental
3381 sequelae assessed at 2 years corrected gestational age (CGA).

3382 **Burden, benefit and risks associated with participation; group relatedness:**

3383 Burden: All infants participating in (either treatment arm of) the study are subjected to
3384 routine neonatal intensive care. The administration of the study intervention itself
3385 (hydrocortisone or placebo administration) does not pose an extra burden on the patients.
3386 This study does not require extra investigations or interventions.

3387 Benefit and risks: Hydrocortisone may facilitate extubation and thereby reduce the total
3388 duration of mechanical ventilation. In addition, hydrocortisone may reduce the incidence of
3389 BPD. Both these beneficial effects may improve neurodevelopmental outcome. On the other
3390 hand, use of hydrocortisone may increase the risk for hyperglycaemia, hypertension,
3391 systemic infection, gastrointestinal perforation and a delay in neurodevelopment. However,
3392 gastrointestinal perforation and delayed neurodevelopment have only been reported in
3393 studies administering corticosteroids in the first week of life and/or during combinations
3394 with other medication. In this study the risk of gastrointestinal perforation and delayed
3395 neurodevelopment may be reduced because hydrocortisone will be administered after the
3396 first week of life and combinations with other drugs will be avoided as much as possible.
3397 Infants assigned to the placebo group will not benefit from the aforementioned possible
3398 beneficial effects nor be subjected to the possible adverse effect of hydrocortisone.

3399 Group relatedness: BPD is a complication occurring exclusively in preterm infants. Any
3400 intervention aiming to reduce the risk of this complication therefore needs to be studied in
3401 this specific population at risk.

3402 **1. BACKGROUND**

3403 Bronchopulmonary dysplasia (BPD) is the most common complication of premature birth,
3404 with a reported incidence of 8% to 35%.^{1,2} BPD is characterized by chronic respiratory
3405 distress, the need for prolonged respiratory support, an increased risk of recurrent
3406 pulmonary infections, airway hyperreactivity during the first years of life³ and life-long
3407 alterations in lung function.⁴⁻⁶ Patients with established BPD have high rates of readmissions
3408 and utilization of health services resulting in tremendous societal costs compared to children
3409 without BPD.⁷⁻⁹ Furthermore, BPD is considered an important risk factor for adverse
3410 neurodevelopmental outcome after premature birth¹⁰⁻¹⁴ with life-long economic and social
3411 consequences.¹⁵⁻¹⁸

3412

3413 In addition to direct mechanical injury, caused by artificial ventilation and oxygen toxicity,
3414 pulmonary inflammation has been identified as an important mediator in the development
3415 of BPD.¹⁹⁻²¹ This is the rationale for treating patients with glucocorticoids, a well known anti-
3416 inflammatory agent. Randomised controlled trials (RCTs) summarized in several systematic
3417 reviews have shown that postnatal systemic glucocorticoids, mainly dexamethasone, reduce
3418 the risk of the combined outcome death or BPD in ventilated preterm infants.²²⁻²⁴

3419 Furthermore, systemic glucocorticoids seem to be most effective when administered in a
3420 time frame of 7 to 14 days postnatal age, the so-called moderately early treatment
3421 onset.^{25,26} However, initiating dexamethasone treatment in the first days of life seems to be
3422 associated with an increased the risk of cerebral palsy (CP). Although this complication has
3423 not been reported by RCTs investigating dexamethasone treatment initiated after the first
3424 week of life, these alarming reports have resulted in a general concern on the use of
3425 dexamethasone in preterm infants.²⁷⁻²⁹ Based on this concern, the American Academy of

3426 Pediatrics, Canadian Paediatric Society, and the European Association of Perinatal Medicine
3427 have stated that clinical trials should be performed to investigate the use of alternative anti-
3428 inflammatory glucocorticoids, such as the less potent glucocorticoid hydrocortisone.^{30,31}
3429
3430 Despite the ongoing concerns on their use, systemic glucocorticoids are still used in
3431 approximately 10% of the preterm infants at risk for BPD.³²⁻³⁴ Dexamethasone is still the
3432 most widely used glucocorticoid drug, but its dose has been significantly reduced and
3433 administration is often postponed until the 3rd or 4th week of life.²⁷
3434
3435 As an alternative, many clinicians have started to use hydrocortisone. Animal data suggest
3436 that hydrocortisone has a less detrimental effect on the brain than dexamethasone.³⁵
3437 However, no placebo controlled RCT has investigated the use of hydrocortisone after the
3438 first week in life in ventilator dependent preterm infants.³⁶ Six RCTs investigating a low
3439 hydrocortisone dose started within < 72 hours after birth (early treatment) failed to show a
3440 clear reduction in the incidence of BPD.³⁷⁻⁴² Only one of these trials reported long-term
3441 follow-up, showing no differences in adverse neurodevelopmental sequelae.⁴³ These
3442 findings are supported by several historical cohort studies, showing no increased risk of
3443 adverse neurodevelopmental outcome in hydrocortisone treated infants.⁴⁴⁻⁴⁶
3444
3445 In most Dutch Neonatal Intensive Care Units (NICUs) preterm infants who are ventilator-
3446 dependent in the second week of life are no longer treated with glucocorticoids. Infants are
3447 kept on the ventilator allowing spontaneous recovery of lung function over time, sometimes
3448 supported by other interventions, such as diuretics and inhalation therapy. With this
3449 approach, some infants can be successfully weaned and extubated. Only those infants that

3450 remain ventilator dependent after 3-4 weeks are treated with glucocorticoids, with the
3451 primary objective to wean and extubate.

3452 Although this approach will undoubtedly result in successful extubation of most infants with
3453 the lowest possible use of glucocorticoids, the question remains if this is also the best
3454 strategy in reducing the incidence of BPD in preterm infants ventilated after 7 days of life.
3455 This question seems justified and relevant because BPD, and not failure to extubate, is
3456 associated with adverse medium- and long-term outcome. This is the main reason why the
3457 primary outcome of this study is death or BPD and not failure to extubate.

3458

3459 The NICU at the University Medical Center Utrecht has historically used hydrocortisone for
3460 chronically ventilated preterm infants. Retrospective studies seem to indicate that
3461 hydrocortisone is effective in reducing BPD, without causing serious adverse effects.
3462 However, these findings need to be confirmed or refuted by a large randomized placebo
3463 controlled trial. Despite the absence of randomized evidence, three out of the 10 Dutch
3464 NICUs switched from dexamethasone to hydrocortisone. This diversity in treatment between
3465 NICUs is undesirable and has also been debated in the public press.⁴⁷ As a first step to
3466 resolve this diversity in treatment, all 10 Dutch NICUs have indicated that a RCT comparing
3467 hydrocortisone with placebo is urgently needed, an initiative that is also supported by the
3468 Dutch Society of Pediatricians (NVK), giving such a trial top priority. Since the NICUs which
3469 already use hydrocortisone are reluctant or refuse to prescribe dexamethasone as trial
3470 medication, a RCT comparing dexamethasone versus hydrocortisone is not possible.

3471

3472 The optimal dose of hydrocortisone is currently unknown. However, the NICU in Utrecht has
3473 been using a fixed hydrocortisone treatment regimen for several decades now and this

3474 regimen has also been adopted by the other Dutch NICUs using hydrocortisone.
3475 Retrospective studies strongly suggest that this is a safe dose, because it was not associated
3476 with an increased risk of adverse neurological outcome.^{45,48} Comparing hydrocortisone
3477 treated patients with dexamethasone treated patients in other NICUs showed no difference
3478 in the incidence of BPD, suggesting that this dose is equally effective in reducing BPD.⁴⁸
3479 Based on these findings and current clinical practice, we decided to adopt the dosing
3480 regimen from Utrecht for this study.

3481

3482 Based on the current available evidence, the American Academy of Pediatrics has concluded
3483 that: (1) routine use of systemic dexamethasone for the prevention or treatment of CLD in
3484 infants with VLBW is not recommended; (2) outside the context of a randomized, controlled
3485 trial, the use of corticosteroids should be limited to exceptional clinical circumstances. Based
3486 on these recommendation ventilated preterm infants are no longer routinely treated with
3487 postnatal corticosteroids. Furthermore, in exceptional cases treatment is, in most cases,
3488 postponed until after the third week of life. Comparison of hydrocortisone to a placebo is
3489 therefore warranted because standard therapy in the second week of life (7-14 d after birth)
3490 is to wait for spontaneous recovery of lung function. In exceptional clinical circumstances
3491 treatment with a (rescue) open label glucocorticoids is still possible in the current study.
3492 Although based on the above, the *extra* risks for the patients in this study are probably
3493 limited, a data monitoring committee will closely monitor any possible adverse effects and
3494 risks, as also explained in paragraph 9.4.

3495

3496 **2. OBJECTIVE**

3497 To investigate if hydrocortisone is safe and effective in reducing the incidence of the
3498 combined outcome death or BPD at 36 weeks PMA in chronically ventilated preterm infants,
3499 as compared to placebo. This study **does not** aim to successfully extubate ventilator-
3500 dependent preterm infants with the lowest possible use of glucocorticoids (i.e.
3501 hydrocortisone), but to use glucocorticoids as an early intervention (7-14 d after birth) to
3502 reduce the risk of death or BPD in these ventilator-dependent preterm infants. From this
3503 point of view the treatment strategy is fundamentally different from what is currently used
3504 in daily clinical practice.

3505

3506 **3. STUDY DESIGN**

3507 Multicenter randomised double-blind placebo-controlled trial with a total duration of 5 years
3508 conducted in 15 neonatal intensive care units in the Netherlands (n=10) and Belgium (n=5).

3509

3510 **4. STUDY POPULATION**

3511 **4.1 Population eligibility**

3512 Ventilated VLBW infants at high risk for BPD treated in a level III NICU

3513

3514 **4.2 Inclusion criteria**

3515 Preterm infants *with an increased risk of BPD* and:

- 3516 - a gestational age < 30 wks and/or birth weight < 1250 g
- 3517 - ventilator dependency at 7-14 days PNA
- 3518 - *a respiratory index (RI = MAwP x FiO₂) of ≥ 3.0* for more than 12 h/day for at least
3519 48 hours, ensuring adequate oxygen saturation (85-95%) and pCO₂ values in
3520 premature infants (5.0-7.5 kPa).

3521 Note: these targets are used to ensure homogeneous assessment of MAwP and FiO₂ for
3522 patient inclusion among participating centres. *For the same reason, clinician are*
3523 *encouraged to aim for the median value of these targets when assessing the RI.* After
3524 inclusion of the patient in the study, physicians are free to use local targets for
3525 oxygenation and ventilation.

3526

3527 **4.3 Exclusion criteria**

3528 - chromosomal defects (e.g. trisomy 13, 18, 21)

3529 - major **congenital** malformations that:

3530 ○ compromise lung function (e.g. surfactant protein deficiencies, congenital

3531 diaphragmatic hernia)

3532 ○ result in chronic ventilation (e.g. Pierre Robin sequence)

3533 ○ increase the risk of death or adverse neurodevelopmental outcome

3534 (congenital cerebral malformations)

3535 Note: intraventricular haemorrhages, periventricular leucomalacia and

3536 cerebral infarction are not considered **congenital** malformations and

3537 therefore are no exclusion criteria.

3538 - Use of dexamethasone or hydrocortisone for the sole purpose of improving lung

3539 function and respiratory status prior to inclusion

3540

3541 Considerations

3542 Although (suspected or proven) sepsis, pneumonia, necrotizing enterocolitis (NEC) and

3543 patent ductus arteriosus (PDA) are well-known causes of respiratory failure, these diagnoses

3544 are know to be independent risk factors for developing BPD. Therefore, these diagnoses are
3545 **not** considered to be exclusion criteria. The following should be taken into consideration:

3546 10. In ventilator-dependent cases of sepsis and pneumonia the attending physician may
3547 start antibiotics and await the effect on respiratory drive/ pulmonary status for 48
3548 hours. If the patient meets the inclusion criteria after 48 h, he/she is eligible for
3549 inclusion.

3550 11. Trials studying the early use (initiated < 96 hours after birth) of corticosteroids have
3551 shown that treatment with corticosteroids may increase the risk of intestinal
3552 perforation. Speculating on the pathogenesis of this adverse effect, it has been
3553 suggested that the synchronous use of indomethacin and corticosteroids might
3554 explain this finding. However, trials starting dexamethasone between 7-14 d after life
3555 have **not** reported an increased risk of intestinal perforation, despite the fact that
3556 some of these patients were also treated for hemodynamically significant PDA with
3557 indomethacin. In other words, the evidence for a possible adverse effect of the
3558 combined use of corticosteroids and indomethacin/ibuprofen is weak. For this reason
3559 the combined use of corticosteroids and indomethacin/ibuprofen is **NOT** prohibited
3560 within the STOP-BPD trial. However, where possible in the time window of 7-14 days,
3561 we do encourage physicians to treat a hemodynamically significant PDA before
3562 randomizing the patient for the study. To make this feasible physicians are strongly
3563 encouraged to determine the presence of a hemodynamically significant PDA at day
3564 7 of life. This way the patient can, if necessary according to the local protocol, still be
3565 treated with 2 courses of indomethacin / ibuprofen before day 14 of life.
3566 If there is an indication to treat a hemodynamically significant PDA with
3567 indomethacin/ibuprofen after randomization, study medication is **NOT** stopped. Yet,

3568 any synchronous use of indomethacin/ibuprofen and study medication or the
3569 occurrence of an intestinal perforation recorded in the case record form, will
3570 automatically result in so-called **Alert Procedure** (see paragraph 9.4. Such an **Alert**
3571 **Procedure**. This will allow for a close and individual monitoring of possible adverse
3572 effects.

3573 12. If the physician considers extubation not an option because of the general condition
3574 of the infant (e.g. NEC with severe hemodynamic instability and severe abdominal
3575 distension) inclusion in the study can be postponed until the maximum of 14 days
3576 PNA.

3577

3578 **4.4 Sample size calculation**The primary outcome parameter is BPD free survival at 36 weeks
3579 PMA. The a priori risk of death or BPD in preterm infants less than 30 weeks gestation and
3580 ventilated in the second week of life is estimated at 60 – 70%. The meta-analysis on
3581 moderately early dexamethasone treatment estimated an absolute risk reduction (ARR) of
3582 25% (NNT=4) compared with placebo.²⁴ However, there are no data currently available on
3583 the efficacy of hydrocortisone and the suggested cumulative dose in the present study is
3584 considerably lower compared to previously used dexamethasone doses. Since the shown
3585 efficacy of dexamethasone is dependent on the used doses in these trials²⁶, we would
3586 propose a more conservative approach, defining an ARR of 15% or more (NNT=7) as clinically
3587 relevant. With an estimated *a priori* risk for death or BPD at 36 weeks PMA of 60%, a type I
3588 error of 5% (2 tailed) and a power of 80% the number of patients to be included in each
3589 treatment arm would be 175 (total 350). Anticipating a 10% drop out of randomized
3590 patients, 200 patients need to be included in each treatment arm (total 400). Based on a
3591 retrospective analysis of ventilated preterm infants at day 7 of life in the majority of Dutch

3592 NICUs we expect a total of 200 eligible patients each year. With an estimated inclusion rate
3593 of 66% of eligible patients and an inclusion period of 3 years, a total of 400 patients should
3594 be included in the study. For sample size calculation we used Nquery (Statistical Solutions
3595 Ltd., Cork, Ireland).

3596

3597 **5. TREATMENT OF SUBJECTS**

3598 **5.1. Therapeutic details**

3599 5.1.1 Preparation of the trial medication: The infants of the hydrocortisone group will receive
3600 hemisuccinate hydrocortisone 5mg/kg/day Q.I.D for 7 days, followed by 3.75 mg/kg/day
3601 T.I.D. for 5 days, subsequently lowering the frequency by one dose every 5 day. This leads to
3602 a total duration of therapy of 22 days and a cumulative dose of 72.5 mg/kg hydrocortisone
3603 (see appendix 1). The infants in the control group receive saline placebo for the entire 22-day
3604 period in the same frequency as the hydrocortisone group. Both saline and hydrocortisone
3605 schedules will be calculated according to weight on the day of randomisation and not adjusted
3606 to the actual weight during the tapering schedule. *Clinicians are encouraged to administer the*
3607 *study medication intravenously as long as this route of access is required for other reasons. If*
3608 *intravenous access is no longer required for the standard treatment, the study medication can*
3609 *be administered orally using the same solution and dose.*

3610

3611 5.1.2 Adjusting study medication for transient short-term adverse effects: previous studies on
3612 corticosteroids use in the second week of life (mainly dexamethasone) have reported that the
3613 following transient short term side-effects: hyperglycaemia, increased risk of infection, and
3614 hypertension. Hyperglycaemia and infection occur frequently at the NICU as co-morbidity of
3615 preterm birth and its treatment. There is extensive experience in treating these morbidities
3616 with, respectively, insulin and antibiotics. Although the incidence of hyperglycaemia and/or

3617 infection will be closely monitored (secondary endpoints), in case of an event, the study
3618 medication should **NOT** be adjusted.
3619 Hypertension is a much less common morbidity after preterm delivery and antihypertensive
3620 drugs are not routinely used in neonatal care. Corticosteroids induced hypertension is usually
3621 treated and resolved by reducing the dose. So, in case of hypertension, the study medication is
3622 lowered according to appendix 1 if no other treatable cause of hypertension can be identified.
3623 Hypertension is defined as a **systolic** blood pressure > 80 mmHg for infants 24-26 wks, > 90
3624 mmHg for infants 26-28 wks, and > 100 mmHg for infants \geq 28 wks. Data on the time, reason
3625 and dose adjustment will be collected. The presence of hypertension leading to adjustment of
3626 study medication will be reported via the **Alert Procedure** (see paragraph 9.4).

3627

3628 5.1.3 Stop criteria during study protocol medication (treatment failure): In general,
3629 the use of open label hydrocortisone during the 22 day treatment course is strongly
3630 discouraged. Open label hydrocortisone use **may be considered** in the following conditions:

- 3631 3. The pulmonary condition is progressively deteriorating and the respiratory index
3632 (MAwP x FiO₂) is > 10 for more than 6 consecutive hours.
- 3633 4. The pulmonary condition of the patient is stable (RI < 10) but not improving over
3634 time. In these circumstances open label hydrocortisone **may be considered** if the
3635 following conditions are met:
- 3636 a. Extubation was attempted (extubation trial) within 24 hours before considering
3637 open label treatment and this attempt failed.
 - 3638 b. The patient is on study medication for **at least** 10 days (but preferably at a later
3639 time).

3640 The open label hydrocortisone dosage schedule is similar to that used in the study. At that
3641 point in time the study medication is stopped and the patient will be recorded as “treatment

3642 failure". In case of treatment failure the following data will be collected: timing of treatment
3643 failure, ventilator support and settings, type of open label medication, starting date,
3644 cumulative dose and duration of rescue therapy. The patients will be followed as all other
3645 patients until the clinical endpoints occur or until end of follow up.

3646 **The use of open label hydrocortisone will be reported via the Alert Procedure** (see
3647 paragraph 9.4).

3648

3649 5.1.4 Late rescue therapy outside study protocol (late rescue glucocorticoids): Patients still on
3650 mechanical ventilation after completion of the study medication, i.e. day 22, may be treated
3651 with open label hydrocortisone. In such cases the physician should first attempt extubation
3652 before considering open label use. The open label hydrocortisone dosage schedule is similar
3653 to that used in the study (see appendix 1). Data on the starting date, cumulative dose and
3654 duration of rescue therapy are collected.

3655

3656 5.1.5 Anti-hypotensive therapy: In case of persistent hypotension, not (sufficiently)
3657 responding to first line treatment with intravascular volume expansion and inotropes
3658 (dopamine and/or dobutamine) the use of hydrocortisone is allowed in a dose of 3 mg/kg/day
3659 for 5 days. Treatment for hypotension will not be considered as treatment failure. Data on
3660 timing, dose and duration will be collected.

3661

3662 5.1.6 Stress dosing during and after study medication: *Infants treated for a longer period of*
3663 *time with corticosteroids might experience inadequate adrenal response to stress (i.e. surgery*
3664 *or sepsis) for several months after stopping treatment. For this reason corticosteroids*
3665 *treatment is almost always tapered over time, as this minimizes the risk of adrenal*
3666 *insufficiency. Some NICUs consider this risk to be so low, that they will only treat patients*

3667 with corticosteroids if they show signs of adrenal insufficiency (hypotension, hypoglycaemia),
3668 while other NICUs will start **preventive** treatment with corticosteroids in case of stressful
3669 events such as surgery. This study will also allow for a **preventive** stress dose treatment if this
3670 is deemed necessary according to the local protocol of the participating NICU. In other
3671 words, **preventive** treatment with a stress dose is **NOT** mandatory.
3672 It is clear that only the patients receiving hydrocortisone, and not those allocated to placebo
3673 treatment, will potentially benefit from a stress dose of hydrocortisone. For this reason
3674 patients will receive a stress dose identical to their study medication. A separate, second
3675 (stress) randomization procedure will make sure that allocation occurs in a blinded fashion.
3676 When the event occurs after completion of study medication, the prescribed dosing schedule is
3677 5 mg/kg Q.I.D. on the day the event occurs, subsequently lowering the frequency by one dose
3678 every day. This leads to a total duration of stress dosing therapy of 5 days and a cumulative
3679 dose of 15 mg/kg study medication. In case the stress event occurs during study treatment, a
3680 stress dose is only started after the first week of treatment. In that case the actual dose is
3681 increased to 5 mg/kg Q.I.D. and subsequently lowered according to the aforementioned stress
3682 schedule until the actual dose of study medication is once again reached. From that point
3683 onwards the original regimen of study medication will be followed again.
3684 It is important to emphasize that the above mentioned procedure only applies to **preventive**
3685 treatment in case of a stressful event. If a patients shows signs of adrenal insufficiency at any
3686 time during a stressful events, he or she should be treated with open label hydrocortisone
3687 according to the dosing schedule mentioned in this paragraph.
3688 Data on number of courses, timing and dose will be collected.
3689
3690 5.1.7 Inhalation corticosteroids: There is currently insufficient evidence that inhaled
3691 corticosteroids will reduce the risk of death or BPD in preterm infants. Use of inhaled

3692 corticosteroids in the first weeks of life is therefore strongly discouraged. However, its use is
3693 not an exclusion criterion. Data on timing, dose and duration will be collected.

3694

3695 **5.2. Use of co-intervention**

3696 All randomized patients will be treated according to the guidelines of the individual NICUs.
3697 All participating NICUs explore treatable causes of ventilator dependency during the first
3698 week of life, such as patent ductus arteriosus, sepsis and pneumonia as much as possible and
3699 treat these according to the department protocol. Although all of these conditions can be an
3700 alternative cause of respiratory failure, they are known risk factors for developing BPD and
3701 therefore are not considered exclusion criteria.

3702

3703 This trial will monitor the prognostic important co-interventions and conditions, as described
3704 in section 8.2.

3705

3706 **6. INVESTIGATIONAL MEDICINAL PRODUCT**

3707 **6.1 Name and description of investigational medicinal product**

3708 In this multicenter study the investigational medicinal product is hydrocortisone. A detailed
3709 description of hydrocortisone can be found in the summary of product characteristics (SPC)
3710 which is added to this protocol as a separate document.

3711

3712 **6.2 Summary of findings from non-clinical studies**

3713 More details on both hydrocortisone and the placebo used in this study can be found in,
3714 respectively, the summary of product characteristics (SPC) and investigational medicinal
3715 product dossier (IMPD) both added to this protocol as separate documents. In addition to

3716 this information, animal studies have shown that hydrocortisone, in contrast to
3717 dexamethasone, did not increase the risk of adverse effects on the brain when compared to
3718 a placebo.³⁵

3719

3720 **6.3 Summary of findings from clinical studies**

3721 Hydrocortisone has several authorized indications as listed in the SPC on page 1. In preterm
3722 infants, hydrocortisone is used for the following indications: 1) primary or secondary
3723 deficiency of corticosteroids; 2) treatment of hypotension; and 3) anti-inflammatory drug in
3724 developing bronchopulmonary dysplasia (BPD). According to the SPC (page 1) only the first
3725 indication is authorized. The fact that hydrocortisone is used for other unauthorized
3726 indications is not exceptional, because off-label use of medication is more the rule than the
3727 exception in neonatology. In this study, hydrocortisone is used for its anti-inflammatory
3728 properties on the lungs of preterm infants at high risk for BPD ventilated in the second week
3729 of life, aiming to reduce the incidence of BPD. To date, six RCTs investigating a low
3730 hydrocortisone dose started within < 72 hours after birth (early treatment) failed to show a
3731 clear reduction in the incidence of BPD.³⁷⁻⁴² Only one of these trials reported long-term
3732 follow-up, showing no differences in adverse neurodevelopmental sequelae.⁴³ Use of
3733 hydrocortisone after the first week of life with a higher dose has been the standard of care in
3734 4 of the 10 Dutch NICUs. The University Medical Center Utrecht has used hydrocortisone in
3735 an identical treatment schedule as this study for several decades. Several historical cohort
3736 studies have shown that hydrocortisone use for this indication (reduction of BPD) did not
3737 increase the risk of adverse neurodevelopmental outcome.⁴⁴⁻⁴⁶

3738

3739 **6.4 Summary of known and potential risks and benefits**

3740 As studies with hydrocortisone are limited, the assessment of risks and benefits are based on
3741 data obtained from previous RCTs investigating other corticosteroids (mainly
3742 dexamethasone) in ventilated preterm infants at risk for BPD. Based on these studies,
3743 hydrocortisone may facilitate extubation and thereby reduce the total duration of
3744 mechanical ventilation. In addition, hydrocortisone may reduce the incidence of BPD. Both
3745 these beneficial effects may improve neurodevelopmental outcome. On the other hand, use
3746 of hydrocortisone may increase the risk for hyperglycaemia, hypertension, systemic
3747 infection, gastrointestinal perforation and a delay in neurodevelopment. However,
3748 gastrointestinal perforation and delayed neurodevelopment have only been reported in
3749 studies administering corticosteroids in the first week of life and/or during combinations
3750 with other medication. In this study the risk of gastrointestinal perforation and delayed
3751 neurodevelopment may be reduced because hydrocortisone will be administered after the
3752 first week of life and combinations with other drugs will be avoided as much as possible.
3753 Infants assigned to the placebo group will not benefit from the aforementioned possible
3754 beneficial effects nor be subjected to the possible adverse effect of hydrocortisone.

3755

3756 **6.5 Description and justification of route of administration and dosage**

3757 The optimal dose of hydrocortisone is currently unknown. However, the NICU in Utrecht has
3758 been using a fixed hydrocortisone treatment regimen for several decades now and this
3759 regimen has also been adopted by the other Dutch NICUs using hydrocortisone.
3760 Retrospective studies strongly suggest that this is a safe dose, because it was not associated
3761 with an increased risk of adverse neurological outcome.^{45,48} Comparing hydrocortisone
3762 treated patients with dexamethasone treated patients in other NICUs showed no difference
3763 in the incidence of BPD, suggesting that this dose is equally effective in reducing BPD.⁴⁸

3764 Based on these findings and current clinical practice, we decided to adopt the dosing
3765 regimen from Utrecht for this study. More details on the dose regiment and the route of
3766 administration can be found in paragraph 5.1.

3767

3768 **6.6 Preparation and labelling of Investigational Medicinal Product**

3769 Preparation and labelling will be done according to relevant GMP guidelines. Hydrocortisone
3770 (Pharmachemie BV Holland) will be provided via the AMC pharmacy (Dr. M. Kemper) and the
3771 placebo will be manufactured by ACE Pharmaceuticals BV (Zeewolde, the Netherlands). The
3772 SPC of hydrocortisone and the IMPD of the placebo are provided as separate documents. In
3773 addition, we have added an example of labels for the vials and boxes as separate
3774 documents.

3775

3776 **6.7 Drug accountability**

3777 Drug accountability will be according to current GMP guidelines. The “kenniscentrum
3778 geneesmiddelen onderzoek” of the AMC pharmacy will take full responsibility and
3779 supervision of the drug accountability process.

3780

3781 **7. METHODS**

3782 **7.1 Randomisation, blinding and treatment allocation**

3783 Written informed consent has to be obtained from either parents or care-givers prior to
3784 randomisation. In case of ventilator dependency after day 7 of life with a suspected diagnosis
3785 of developing BPD, parents receive the study information as soon as possible allowing them
3786 sufficient time to consider participation. The actual decision to include the patient in the trial
3787 should be made between day 7 and 14 PNA. Following inclusion and randomization, the first

3788 dose of study medication should be administered within 24 hours. Randomization will be
3789 centrally controlled and web-based using a computer program designed for this study. This
3790 trial will be protected from selection bias by using concealed, stratified and blocked
3791 randomisation.
3792
3793 Randomisation will be per center and stratified according to gestational age stratum (Stratum
3794 A: < 27 weeks; Stratum B: \geq 27 weeks), in order to achieve an equal distribution in both
3795 treatment arms. The allocation ratio will be 1:1 with block randomisation using variable block
3796 sizes. Multiple birth infants will be randomised independently, unless the parents or
3797 caretakers explicitly demand that the siblings should be treated according to the same
3798 treatment arm. An automated mechanism to perform twin randomisation is in place.
3799 The infants' parents and all members of the medical team, including investigators, remain
3800 blinded to group assignment throughout the study.
3801
3802 Patient characteristics, including gestational age, birth weight and respiratory status, will be
3803 collected from all eligible infants that are not included in the study. In addition, we will
3804 collect data on why the patients were not included. With this information we will assess
3805 possible bias in patient inclusion.
3806
3807 **7.2 Withdrawal of individual subjects**
3808 Parents or caregivers can leave the study at any time for any reason if they wish to do so
3809 without any consequences.
3810 Note: patients who are considered to have "treatment failure" based on the prespecified
3811 criteria (paragraph 5.1.3) are **NOT** withdrawn from the study, and remain in follow up.
3812

3813 **7.3 Replacement of individual subjects after withdrawal**

3814 The number of withdrawn patients not marked as prespecified treatment failure (see section
3815 7.2) will be replaced.

3816

3817 **7.4 Follow-up of subjects withdrawn from treatment**

3818 Subjects withdrawn from the study will be treated according to the standard of care, including
3819 neurodevelopmental outcome assessment at the outpatient clinic.

3820

3821 **7.5 Premature termination of the trial**

3822 An independent *Data Monitoring Committee (DMC)* will monitor the study on safety aspects
3823 (see section 9.4) and if necessary recommend termination of the study.

3824

3825 **7.6 Breaking the randomization code**

3826 Unblinding is only performed in emergency situations where knowledge of the identity of the
3827 study drug is considered absolutely necessary for the clinical management of the subject. If
3828 local investigator or attending physician decides unblinding is essential, (s)he will make every
3829 effort to contact the PI before unblinding to discuss options. For this purpose a 24/7 reachable
3830 telephone service will be installed. Details of the unblinding procedure will be defined in the
3831 study specific working instructions.

3832

3833 **7.7. Endpoints**

3834 7.7.1. Primary endpoint: the dichotomous variable *BPD free survival at 36 weeks PMA*. BPD
3835 at 36 weeks PMA will be assessed according to the NIHCHD Consensus Statement defining
3836 normal oxygen saturation as 86%-94%. The severity of the BPD will be assessed as proposed
3837 by Jobe et.al.²¹, since the severity of BPD has a high association with neurodevelopmental

3838 sequelae.¹² In case of supplemental oxygen delivery >21% and < 30% or low flow at 36 weeks
3839 PMA, the oxygen reduction test as described by Walsh et.al.^{21,49,50} should be performed. A
3840 positive oxygen reduction test has a high correlation with the risk on discharge home with
3841 oxygen, the length of hospital stay, and pulmonary morbidity requiring hospital readmission
3842 during the first year of life. For practical guidance on the use of the oxygen reduction test
3843 please go to appendix 2.

3844

3845 7.7.2. Secondary endpoints:

- 3846 • treatment failure as defined in section 5.1.3
- 3847 • mortality at 28 days PNA, 36 weeks PMA and at hospital discharge
- 3848 • BPD at 28 days
- 3849 • failure to extubate 3, 7, 14 and 21 days after initiating therapy
- 3850 • duration of mechanical ventilation
- 3851 • use of “rescue treatment” with hydrocortisone outside the study protocol
- 3852 • total time on supplemental oxygen
- 3853 • length of hospital stay
- 3854 • incidence of hypertension, as defined in paragraph 5.1.2
- 3855 • hyperglycaemia requiring the use of insulin therapy
- 3856 • nosocomial infection, like sepsis, meningitis and pneumonia
- 3857 • pulmonary hemorrhage, pneumothorax and pulmonary interstitial emphysema
- 3858 • hemodynamic significant patent ductus arteriosus for which medical intervention or
3859 surgical ligation is needed
- 3860 • necrotising enterocolitis (NEC), diagnosed at surgery, autopsy or by radiographic
3861 finding of pneumatosis intestinalis or hepatobiliary gas (Bell stage II)

- 3862 • gastrointestinal bleeding
- 3863 • isolated gastrointestinal perforation diagnosed on abdominal radiography
- 3864 • intraventricular haemorrhage (IVH) and/or periventricular leucomalacia (PVL),
- 3865 including grading on cerebral ultrasonography according to protocol defined by Ment
- 3866 et.al.⁵¹
- 3867 • retinopathy of prematurity, including grading following international classification⁵²
- 3868 • weight, head circumference and length at 36 weeks PMA
- 3869 • long-term health and neurodevelopmental sequelae, assessed at 2 years c.a.:
- 3870 ○ readmissions since first discharge home
- 3871 ○ weight, length and head circumference at 24 months c.a.
- 3872 ○ Bayley Scales of Infant Development III, Mental Developmental Index and
- 3873 Psychomotor Developmental Index
- 3874 ○ cerebral palsy and severity of cerebral palsy using gross motor function
- 3875 classification system
- 3876 ○ hearing loss requiring hearing aids
- 3877 ○ blindness
- 3878 ○ behavioural problems (child behaviour checklist)

3879

3880 All primary and secondary endpoints are measured as part of standard usual care in the
3881 Netherlands and Belgium, and will be derived from the charts of the patients by the
3882 investigators.

3883 **8. DATA COLLECTION AND STATISTICAL ANALYSIS**

3884 **8.1 Baseline characteristics**

3885 Baseline characteristics are collected prior to inclusion and randomization with respect to the
3886 following baseline characteristics: demographic details and patient characteristics, such as
3887 gestational age, small for gestational age, antenatal problems, antenatal steroids, surfactant
3888 therapy, mode of delivery, resuscitation details, Apgar scores, presence of IVH/PVL, and
3889 occurrence of PDA. Base line characteristics on ventilator settings, gas exchange will be
3890 collected on day of randomization.

3891

3892 **8.2 Co-interventions**

3893 Apart from the study medication all patients will receive standard care, including co-
3894 medication such as surfactant, inhaled nitric oxide, methylxanthines, vitamin A, antibiotics,
3895 antimycotic therapy, diuretics, ibuprofen/indomethacine, inotropes, and inhaled
3896 corticosteroids. These co-medications are prescribed on the basis of (inter)national guidelines
3897 and/or local protocols. Since the route of administration (e.g. oral or IV), the dose and
3898 frequency may vary continuously depending on the weight and the clinical condition of the
3899 patients, only name, start and stop date are recorded in the CRF. For all other drugs used
3900 during the admission data will be recorded according to GCP guidelines.

3901 Also the ventilation mode with the ventilator settings will be recorded and analyzed.

3902

3903 **8.3 Statistical analysis**

3904 Normally distributed data will be presented as mean \pm standard deviations, not-normally
3905 distributed data as medians and (interquartile) ranges. Categorical data will be analysed
3906 using the Chi-square test. Continuous data will be analysed using the Student's *t* test or
3907 Mann-Whitney test as appropriate. Both intention-to-treat and per-protocol analysis will be
3908 employed. The effect of hydrocortisone on the primary outcome death or BPD will be

3909 assessed by multi-variable logistic regression analysis including possible confounders.

3910 Statistical significance is set at $p < 0.05$.

3911

3912 **9. SAFETY REPORTING**

3913 **9.1 Section 10 WMO (Wet Medisch-wetenschappelijk Onderzoek met Mensen)**

3914 In accordance with section 10, subsection 1, of the Dutch WMO, the investigator will inform
3915 the subjects' parents or caregivers and the reviewing accredited METC (*Medisch Ethische*
3916 *Toetsingscommissie*) if anything occurs, on the basis of which it appears that the
3917 disadvantages of participation may be significantly greater than was foreseen in the research
3918 proposal. The study will be suspended pending further review by the accredited METC,
3919 except insofar as suspension would jeopardise the subjects' health. The investigator will
3920 ensure that all subjects' parents or caregivers are kept informed.

3921

3922 **9.2 Adverse and serious adverse events (SAE)**

3923 Adverse events are defined as any undesirable experience occurring to a subject during a
3924 clinical trial, whether or not considered related to the investigational drug. All adverse
3925 events observed by the investigator or his staff will be recorded. A **serious adverse event** is
3926 any untoward medical occurrence or effect that at any dose

3927 - results in death;

3928 - is life threatening (at the time of the event);

3929 - requires hospitalization or prolongation of existing inpatients' hospitalization;

3930 - results in persistent or significant disability or incapacity;

3931 - is a congenital anomaly or birth defect (not applicable in this trial);

3932 - other important events that may jeopardize the safety of the subject or may require

3933 intervention to prevent one of the outcomes listed above.

3934

3935 All SAEs will be reported, as described below (9.2.1), by the principle investigator to the Data
3936 Monitoring Committee (DMC) and to the accredited METC that approved the protocol,
3937 according to the requirements of that METC.

3938

3939 9.2.1 Context-specific SAE reporting

3940 This study population (critically ill preterm infants) has a high risk of serious complications
3941 (so-called “context-specific SAE’s”), which are inherent to their vulnerable condition and
3942 unrelated to the intervention which is under evaluation in this trial.

3943 These complications are included in the primary and secondary outcomes of this study and
3944 are recorded in the Case Report Form. This documentation will include the date of diagnosis,
3945 classification/gradation of the complication, type of action taken if appropriate (with some
3946 complications a wait and see approach is warranted). Since these complications are highly
3947 interrelated and of longitudinal character, it is impossible to indicate an exact date for the
3948 resolution or stabilisation of each specific diagnosis. Therefore, we will use the date of
3949 discharge from the NICU for this purpose. As long as the child is admitted to the NICU, the
3950 complication will be classified as ongoing.

3951 In light of the above, immediate and individual reporting of all these condition related
3952 complications will not enhance the safety of study.^{1,2} This is also in accordance with CCMO
3953 regulations (<http://www.ccmo-online.nl/main.asp?pid=25&sid=49&ssid=178>)

3954 The context-specific SAEs that will be identified include the events listed under paragraph
3955 7.7.2, on page 27 and 28 of the protocol.

3956 Once a year, an overview of the aforementioned complications for each treatment arm and
3957 ordered by organ system will be presented to the DMC and METC. This overview will consist
3958 of the following information: name of the complication, date of diagnosis,
3959 classification/gradation of the complication, type of action taken, date of discharge or
3960 ongoing.^{53,54}

3961 9.2.2 Suspected unexpected serious adverse reactions (SUSAR)

3962 Adverse reactions are all untoward and unintended responses to an investigational product
3963 related to any dose administered.

3964

3965 Unexpected adverse reactions are adverse reactions, of which the nature, or severity, is not
3966 consistent with the applicable product information (see SPC/IMPDP) or the context-specific
3967 SAEs listed in paragraph 9.2.1.

3968

3969 Any SUSAR should be reported, as soon as it occurs, to the principle investigator and the
3970 study coordinator via the study website (**Alert Procedure**, see paragraph 9.4). The PI will
3971 report expedited all SUSARs through the web portal ToetsingOnline to the METC, competent
3972 authority, Medicine Evaluation Board as well as to the competent authorities in other
3973 Member States, according to the requirements of the Member States.

3974 The expedited reporting will occur not later than 15 days after the PI has first knowledge of
3975 the adverse reactions. For fatal or life threatening cases the term will be maximal 7 days for
3976 a preliminary report with another 8 days for completion of the report.

3977

3978 9.2.3 Annual safety report

3979 In addition to the expedited reporting of SUSARs, the PI will submit, once a year throughout
3980 the clinical trial, a safety report to the DMC, accredited METC, competent authority,
3981 Medicine Evaluation Board and competent authorities of the concerned Member States as
3982 well as the investigators of all participating centers.

3983 This safety report consists of:

- 3984 – a list of all suspected (unexpected or expected) serious adverse reactions, along with an
3985 aggregated summary table of all reported serious adverse reactions
- 3986 – a report concerning the safety of the subjects, consisting of a complete safety analysis
3987 and an evaluation of the balance between the efficacy and the harmfulness of the
3988 medicine under investigation.

3989

3990 **9.3 Follow-up of adverse events**

3991 All adverse events will be followed until they have abated, or until a stable situation has
3992 been reached. Depending on the event, follow up may require additional tests or medical
3993 procedures as indicated. According to the standard of care, all infants will participate in the
3994 usual NICU follow-up program. This program is targeted at evaluating and coordinating
3995 diagnostic procedures and treatment of all prematurity related problems, in close
3996 cooperation with regional and local pediatricians.

3997

3998 **9.4 Data Monitoring Committee (DMC), the Alert Procedure**

3999 An external Data Monitoring Committee (DMC) will monitor efficacy and safety outcomes
4000 and will provide the trial's Steering Committee with recommendations regarding continuing
4001 or stopping the trial (for all patients or subgroups of patients) when approximately 25%
4002 (safety only), 50% (safety and efficacy) and 75% (safety and efficacy) of the anticipated

4003 outcome data are available. Data summaries for the DMC will be prepared by a statistician
4004 who is not a member of the investigating team. The safety data will include, but not be
4005 restricted to, serious adverse events and the safety outcomes listed as secondary outcomes.
4006 The DMC will be blinded to the treatment allocation. During the closed DMC meetings, the
4007 data manager will be stand-by to reveal the allocation labels if the DMC thinks this is
4008 necessary. If the DMC recommends modification or cessation of the study protocol, this will
4009 be discussed with the Steering Committee, who will make the decision. The DMC will be
4010 composed of 3 individuals: a neonatologist with extensive knowledge of BPD, a statistician
4011 who has experience with trials, and some experience on previous DMCs and a
4012 pharmacologist with extensive knowledge of the use of hydrocortisone (corticosteroids) in
4013 neonates. The Steering Committee will propose a detailed mandate and review this with the
4014 DMC, from the outset. Identification and circulation of external evidence (e.g., from other
4015 trials/systematic reviews) is not the responsibility of the DMC members. It is the
4016 responsibility of the PI to provide any such information to the DMC.

4017

4018 To enhance the safety of patients in the STOP-BPD trial, a special alert procedure has been
4019 added to the CRF and the website (SUSAR), “The Alert Procedure”. This tool is used to
4020 monitor special conditions and acute situations that need the direct attention of the
4021 principle investigator and the study coordinator. If necessary the Steering Committee can
4022 decide to alert the DMC. Furthermore, the Steering Committee will provide a summary
4023 report after every 10 alerts to the DMC.

4024

4025 There are 5 situations when the **Alert Procedure** must be used:

4026 6. Any synchronous use of indomethacin/ibuprofen and study medication

4027 7. Any intestinal perforation occurring during or after the study medication treatment

4028 course

4029 8. Occurrence of hypertension as defined

4030 9. Any use of open label hydrocortisone

4031 10. Occurrence of a SUSAR

4032

4033 The "Alert Procedure" will run in the background for the first 4 conditions. CRF data will be

4034 linked automatically and an email will be send to principal investigator and the study

4035 coordinator automatically once conditions 1 to 4 occur. In case of a SUSAR the local

4036 investigator can alert the principal investigator and the study coordinator via a SUSAR email

4037 button on the trial website.

4038

4039 **10. ETHICAL CONSIDERATIONS**

4040 **10.1 Regulation statement**

4041 The study will be conducted according to the principles of the Declaration of Helsinki⁵⁵ and

4042 in accordance with the Medical Research Involving Human Subjects Act (WMO).

4043

4044 **10.2 Recruitment and informed consent**

4045 Patients will be recruited and their parents will be informed and asked for consent by the

4046 attending paediatricians. Informed written consent must be obtained from the parents prior to

4047 randomisation for the study. The patient information letter and informed consent are provided

4048 in section I of the study dossier. The right of a parent or patient to refuse participation without

4049 giving reasons will be respected. The parents will remain free to withdraw their child at any

4050 time from the study without consequences for further treatment.

4051

4052 **10.3 Benefits and risks assessment, group relatedness**

4053 Burden: All infants participating in (either treatment arm of) the study are subjected to
4054 routine neonatal intensive care. The administration of the study intervention itself
4055 (hydrocortisone or placebo administration) does not pose an extra burden on the patients
4056 since intravenous access will be necessary for other clinical reasons. If this is no longer the
4057 case, study medication may be administered via the oral route. This study does not require
4058 extra investigations or interventions.

4059 Benefit and risks: Hydrocortisone may facilitate extubation and thereby reduce the total
4060 duration of mechanical ventilation. In addition, hydrocortisone may reduce the incidence of
4061 BPD. Both these beneficial effects may improve neurodevelopmental outcome. On the other
4062 hand, use of hydrocortisone may increase the risk for (often transient) hyperglycemia,
4063 hypertension and systemic infection. Although the increased risk of gastrointestinal
4064 perforation has up to now only been reported during the early (within the first 96 hours of
4065 life) administration of corticosteroids, the risk may also be increased when administering
4066 hydrocortisone after the first week of life. Finally, early (within the first 96 hours of life) use
4067 of dexamethasone has been associated with an increase risk for neurodevelopmental
4068 sequelae. Historical cohort studies investigating the use of hydrocortisone after the first
4069 week of life have found no evidence to support this. Infants assigned to the placebo group
4070 will not benefit from the aforementioned possible beneficial effects nor be subjected to the
4071 possible adverse effect of hydrocortisone.

4072 Group relatedness: BPD is a complication occurring exclusively in preterm infants. Any
4073 intervention aiming to reduce the risk of this complication therefore needs to be studied in
4074 this specific population at risk.

4075

4076 **10.4 Compensation for injury**

4077 The sponsor/investigator has a liability insurance which is in accordance with article 7,
4078 subsection 6 of the WMO. The sponsor (also) has an insurance which is in accordance with
4079 the legal requirements in the Netherlands (Article 7 WMO and the Measure regarding
4080 Compulsory Insurance for Clinical Research in Humans of 23rd June 2003). This insurance
4081 provides cover for damage to research subjects through injury or death caused by the study.
4082 1. € 450.000,-- (i.e. four hundred and fifty thousand Euro) for death or injury for each
4083 subject who participates in the Research;
4084 2. € 3.500.000,-- (i.e. three million five hundred thousand Euro) for death or injury for all
4085 subjects who participate in the Research;
4086 3. € 5.000.000,-- (i.e. five million Euro) for the total damage incurred by the organization
4087 for all damage disclosed by scientific research for the Sponsor as ‘verrichter’ in the
4088 meaning of said Act in each year of insurance coverage.
4089 The insurance applies to the damage that becomes apparent during the study or within 4 years
4090 after the end of the study.

4091

4092 **10.5 Incentives**

4093 Participants will not receive a financial compensation for participation as an incentive.

4094

4095 **11. ADMINISTRATIVE ASPECTS AND PUBLICATION**

4096 **11.1 Handling and storage of data and documents**

4097 Datamanagement will be implemented according to Good Clinical Practice (GCP)-guidelines.
4098 Patient data will be entered by way of an eCRF in a central GCP proof internet based
4099 database to facilitate on-site data-entry. Security is guaranteed with login names, login

4100 codes and encrypted data transfer. An experienced datamanager will maintain the database
4101 and check the information in the database for completeness, consistency and plausibility.

4102

4103 The data of all subjects will be coded and this coding will not be retraceable to the individual
4104 patient. The key to this coding is safeguarded by the investigator. A limited number of
4105 people have access to the source data. These are the principal investigator, investigating
4106 doctor and investigating personnel. Personal data are only processed by the researchers or
4107 by those who fall directly under their authority. In addition, the study monitor, quality
4108 assurance auditor, employees from the METC and the Health Care Inspectorate of the
4109 Ministry of Health, welfare and Sport (Nederlandse Inspectie voor de Gezondheidszorg) have
4110 access to the source data. All are subject to the pledge of confidentiality. Data and human
4111 material will be stored for 15 years strictly confidential.

4112

4113 **11.2 Amendments**

4114 Amendments are changes made to the trial after a favourable opinion by the accredited METC
4115 has been given. All amendments will be notified to the METC that gave a favourable opinion.
4116 All substantial amendments will be notified to the METC and to the competent authority.
4117 Non-substantial amendments will not be notified to the accredited METC and the competent
4118 authority, but will be recorded and filed by the Steering Committee.

4119

4120 **11.3 Annual progress report**

4121 If requested, an annual progress report of the progress of the trial will be provided to the
4122 accredited METC. Information will be provided on the date of inclusion of the first subject,
4123 numbers of subjects included and numbers of subjects that have completed the trial, serious
4124 adverse events/ serious adverse reactions, other problems, and amendments. In case the study

4125 is ended prematurely, the investigator will notify the accredited METC, including the reasons
4126 for the premature termination. Within one year after the end of the study, the
4127 investigator/sponsor will submit a final study report with the results of the study, including
4128 any publications/abstracts of the study, to the accredited METC.

4129

4130 **11.4 Public disclosure and publication policy**

4131 The study will be registered in the EUDRACT, the website of the Dutch National Competent
4132 Authority, the 'Centrale Commissie Mensgebonden Onderzoek' (CCMO), Dutch public trial
4133 registry, part of the WHO registry. The results of the study will be published in peer-
4134 reviewed international medical journals. In addition, the results of the study will be used for
4135 development and implementation of a guideline on treatment of BPD, which will benefit
4136 future patients.

4137

4138 **12. ORGANISATION**

4139 **12.1 Steering Committee**

4140 The Steering Committee is the main policy and decision making committee of the study and
4141 has final responsibility for the scientific conduct of the study. It will be composed of
4142 representatives of the sponsor, of the investigators of the participating centres and of the
4143 MCRN. The specific tasks of the Steering Committee are:

- 4144 • Approve the study protocol
- 4145 • Approve necessary changes in the protocol based on considerations of feasibility
- 4146 • Act upon recommendations of the Data Monitoring Committee
- 4147 • Review performance reports of the study sites
- 4148 • Resolve operational problems brought before it by the project manager

- 4149 • Approve study reports and papers for publication.

4150

4151 **12.2 Data Monitoring Committee**

4152 An independent Data Monitoring Committee (DMC) will be created specifically for this trial.

4153 The DMC will act in advisory capacity to the Steering Committee. See Paragraph 9.4 for a

4154 description of the membership, tasks and responsibilities of the DMC.

4155

4156 **12.3 Clinical Project Manager / Central Study Coordinator**

4157 An experienced clinical project manager (CPM) from MCRN will manage the quality of the

4158 study according to the Good Clinical Practice (GCP)-guidelines, supervise the data monitoring

4159 process, and verify the quality of conduct of all study personnel. The CPM and/or clinical

4160 research associate (CRA) will arrange that the study personnel is adequately trained in GCP

4161 and study protocol, where needed. The CPM meets regularly with the CRA, data managers,

4162 the Data Safety Monitoring Committee (DSMC), financial departments of study centers, and

4163 all other relevant parties to assure study progress, quality and financials are according to

4164 planning. The CPM will coordinate regulatory authority and ethics committee submissions.

4165 The CPM provides regularly an overall study status report to the Steering Committee

4166

4167 **12.4 Study Monitoring**

4168 The study will be monitored by an experienced monitor from MCRN throughout its duration

4169 by means of personal visits to the Investigator's facilities and through other communications

4170 (e.g., telephone calls, written correspondence).

4171 Monitoring visits will be scheduled at mutually agreeable times periodically throughout the

4172 study and at frequency deemed appropriate for the study.

4173 These visits will be conducted to evaluate the progress of the study, ensure the rights and
4174 wellbeing of the subjects are protected, check that the reported clinical study data are
4175 accurate, complete and verifiable from source documents, and the conduct of the study is in
4176 compliance with the approved protocol and amendments, GCP and applicable national
4177 regulatory requirements. A monitoring visit will include a review of the essential clinical
4178 study documents (regulatory documents, CRFs, source documents, drug disposition records,
4179 subject informed consent forms, etc.) as well as discussion on the conduct of the study with
4180 the Investigator and staff. The Investigator and staff should be available during these visits to
4181 facilitate the review of the clinical study records and resolve/document any discrepancies
4182 found during the visit.

4183

4184 **12.5 Quality Assurance Audits and Inspections**

4185 The Sponsor's (or an authorized representative's) Quality Assurance department may conduct
4186 audits of all aspects of the clinical study either during the study or after the study has been
4187 completed. By participating this trial the investigator agrees to this requirement.

4188 The clinical study may also be subject to inspection by regulatory authorities as well as the
4189 accredited Medical Ethical Committee/ Competent authority to ascertain that the study is
4190 being or has been conducted in accordance with protocol requirements, GCP, as well as the
4191 applicable regulatory requirements.

4192

4193

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4352

APPENDIX 1 STUDIE MEDICATIE SCHEMA

| Step 1: Fill in patient data in yellow cubicles. Use weight at day of randomization. | | Step 2: Fill in date and time of first administration study medication in green cubicle. Format for filling date/time: dd-mm-yyyy hr:mm | | Step 3: In case of hypertension related to study medication, fill in the red cubicle. The program will automatically skip the next dose and commence the following dose with a lower daily frequency. | | Step 4: For print out of study medication list, press: <input type="button" value="Print"/> | | | |
|--|--|---|----------|---|----------------|---|---------------|----------|---------------|
| Study identification | | First administration | | | |  | | | |
| Name | | Date/time | | | | | | | |
| Date of birth | | Lowering dosage regimen | | | | | | | |
| Weight | | Date/time | | | | | | | |
| gram | | | | | | | | | |
| Day in regimen | Time | Times per day | mg/dose | Daily dose/kg | Day in regimen | Time | Times per day | mg/dose | Daily dose/kg |
| Day 1 | 0-01-00 0:00 0-01-00 6:00 0-01-00 12:00 0-01-00 18:00 | 4 x | 0.00 mg. | 5 mg/kg/d | Day 8 | 7-01-00 0:00 7-01-00 8:00 7-01-00 16:00 | 3 x | 0.00 mg. | 3.75 mg/kg/d |
| Day 2 | 1-01-00 0:00 1-01-00 6:00 1-01-00 12:00 1-01-00 18:00 | 4 x | 0.00 mg. | 5 mg/kg/d | Day 9 | 8-01-00 0:00 8-01-00 8:00 8-01-00 16:00 | 3 x | 0.00 mg. | 3.75 mg/kg/d |
| Day 3 | 2-01-00 0:00 2-01-00 6:00 2-01-00 12:00 2-01-00 18:00 | 4 x | 0.00 mg. | 5 mg/kg/d | Day 10 | 9-01-00 0:00 9-01-00 8:00 9-01-00 16:00 | 3 x | 0.00 mg. | 3.75 mg/kg/d |
| Day 4 | 3-01-00 0:00 3-01-00 6:00 3-01-00 12:00 3-01-00 18:00 | 4 x | 0.00 mg. | 5 mg/kg/d | Day 11 | 10-01-00 0:00 10-01-00 8:00 10-01-00 16:00 | 3 x | 0.00 mg. | 3.75 mg/kg/d |
| Day 5 | 4-01-00 0:00 4-01-00 6:00 4-01-00 12:00 4-01-00 18:00 | 4 x | 0.00 mg. | 5 mg/kg/d | Day 12 | 11-01-00 0:00 11-01-00 8:00 11-01-00 16:00 | 3 x | 0.00 mg. | 3.75 mg/kg/d |
| Day 6 | 5-01-00 0:00 5-01-00 6:00 5-01-00 12:00 5-01-00 18:00 | 4 x | 0.00 mg. | 5 mg/kg/d | Day 13 | 12-01-00 0:00 12-01-00 12:00 | 2 x | 0.00 mg. | 2.5 mg/kg/d |
| Day 7 | 6-01-00 0:00 6-01-00 6:00 6-01-00 12:00 6-01-00 18:00 | 4 x | 0.00 mg. | 5 mg/kg/d | Day 14 | 13-01-00 0:00 13-01-00 12:00 | 2 x | 0.00 mg. | 2.5 mg/kg/d |
| | | | | | Day 15 | 14-01-00 0:00 14-01-00 12:00 | 2 x | 0.00 mg. | 2.5 mg/kg/d |
| | | | | | Day 16 | 15-01-00 0:00 15-01-00 12:00 | 2 x | 0.00 mg. | 2.5 mg/kg/d |
| | | | | | Day 17 | 16-01-00 0:00 16-01-00 12:00 | 2 x | 0.00 mg. | 2.5 mg/kg/d |
| | | | | | Day 18 | 17-01-00 0:00 | 1 x | 0.00 mg. | 1.25 mg/kg/d |
| | | | | | Day 19 | 18-01-00 0:00 | 1 x | 0.00 mg. | 1.25 mg/kg/d |
| | | | | | Day 20 | 19-01-00 0:00 | 1 x | 0.00 mg. | 1.25 mg/kg/d |
| | | | | | Day 21 | 20-01-00 0:00 | 1 x | 0.00 mg. | 1.25 mg/kg/d |
| | | | | | Day 22 | 21-01-00 0:00 | 1 x | 0.00 mg. | 1.25 mg/kg/d |

4353

4354 **APPENDIX 2**

4355

4356 **Oxygen reduction test**

4357 Bronchopulmonary dysplasia (BPD) can be classified in to mild, moderate or severe
4358 depending on the amount and duration of supplemental oxygen and the level of respiratory
4359 support. If a patient has received supplemental oxygen for more than 28 d ($FiO_2 > 0.21$ for
4360 more than 12 hours each day) and is receiving no extra oxygen at 36 weeks postmenstrual
4361 age (PMA), he or she is classified as having mild BPD. If the oxygen need at 36 weeks PMA is
4362 between 0.21 and 0.30, BPD is classified as moderate and in case of a $FiO_2 > 0.30$ and/or
4363 receiving continuous positive airway pressure (nCPAP)/mechanical ventilation as severe.

4364 It is important to realize that the duration of supplemental oxygen is highly dependent on
4365 target ranges of transcutaneous oxygen saturation (SpO_2) and the alertness of the clinician
4366 to actively wean oxygen delivery.

4367 To make sure that patients receive supplemental oxygen for pulmonary reasons and to
4368 standardize the amount of oxygen to predefined and uniform SpO_2 targets, Walsh et al.
4369 developed a so-called oxygen reduction test at 36 weeks PMA. Patients are eligible for
4370 testing if they need a FiO_2 between 0.21 and 0.30 to maintain the SpO_2 between 90-96% **or** if
4371 they receive a $FiO_2 > 0.30$ resulting in a $SpO_2 > 96\%$. Patients supported with nasal cannulae
4372 (flow not nCPAP) without supplemental oxygen, and patients treated with
4373 nCPAP/mechanical ventilation or with a $FiO_2 > 0.30$ resulting in a $SpO_2 < 96\%$ do not need
4374 additional testing, and are, respectively, classified as having mild and severe BPD.

4375 ***The oxygen reduction test***4376 **Indications:**

4377 - $\text{FiO}_2 > 0.21$ and < 0.30 with oxygen saturation ranges between 90% and 96%

4378 - $\text{FiO}_2 > 0.30$ with a oxygen saturation range above 96%

4379 Methods:

4380 The patient is placed in supine position and the test is initiated 30 minutes after a feeding. The

4381 supplemental oxygen requirement will be gradually weaned to room air while monitoring

4382 SpO_2 . The diagnosis moderate BPD can be rejected when the SpO_2 remain above $\geq 88\%$ in

4383 room air during 1 hour without apnea or bradycardia.

4384 The diagnosis moderate BPD is confirmed if the saturation goes below 80% during > 1 minute

4385 or remains between 80-87% during > 5 minutes. All occurrences of movement artifact

4386 (defined as visible motion of the infant together with loss of plethysmograph signal from the

4387 monitor) are recorded and corresponding saturation values are to be deleted.

4388

4389 The test contains 4 phases

4390 Phase 1: Baseline evaluation

4391 For 15 minutes heart rate, respiratory rate, SpO_2 , number of apnea (cessation of breathing $>$

4392 20 seconds) and bradycardia (heart rate $< 80/\text{min}$ during > 10 sec) will be collected.

4393 Phase 2: Oxygen reduction

4394 The supplemental oxygen will be weaned by 2% to room air, after which the flow will be

4395 weaned with 0.1 L/min to 0 L/min; The nasal cannulae will be removed from the nares, but

4396 not removed from the face.

4397 Phase 3: Observation period

4398 For the period of 1 hour the heart rate, respiratory rate, and SpO_2 in room air will be

4399 registered. In case of a desaturation below 80% for > 1 minute or saturation between 80-87%

4400 for > 5 minutes, the supplemental oxygen will be restarted and the test will be aborted.

4401 *Phase 4: Back to situation before the test*

4402 The level of supplemental oxygen and flow will be reset to the status before the test.

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4450 PROTOCOL

4451 **Systemic Hydrocortisone To Prevent Bronchopulmonary Dysplasia in preterm**4452 **infants: the SToP-BPD study**4453 **A multicenter randomised placebo controlled trial**

| | |
|-------------------------------|---|
| Protocol ID | Systemic Hydrocortisone To Prevent Bronchopulmonary Dysplasia in preterm infants: the SToP-BPD study |
| Short title | Hydrocortisone for bronchopulmonary dysplasia |
| Version | 5 |
| Date | 11 November 2012 |
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4528 **LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS**

4529

| | | |
|------|---------|--|
| 4530 | ARR | Absolute Risk Reduction |
| 4531 | BPD | BronchoPulmonary Dysplasia |
| 4532 | BW | Birth Weight |
| 4533 | CDP | Continuous Distension Pressure |
| 4534 | CGA | Corrected Gestational Age |
| 4535 | CP | Cerebral Palsy |
| 4536 | DNRN | Dutch Neonatal Research Netwerk; in Dutch: Nederlands Neonataal |
| 4537 | | Research Netwerk (NNRN) |
| 4538 | DMC | Data Monitoring & Safety Committee |
| 4539 | ESEMC | External Safety and Efficacy Monitoring Committee |
| 4540 | GA | Gestational Age |
| 4541 | HFO | High Frequency Oscillation |
| 4542 | IMP | Investigational Medicinal Product |
| 4543 | IVH | IntraVentricular Haemorrhage |
| 4544 | MAwP | Mean Airway Pressure |
| 4545 | METC | Medical research ethics committee (MREC); in Dutch: Medisch |
| 4546 | | Ethische Toetsing Commissie |
| 4547 | MRI | Magnetic Resonance Imaging |
| 4548 | NEC | Necrotising EnteroColitis |
| 4549 | NICU | Neonatal Intensive Care Unit |
| 4550 | NICHD | National Institutes for Child Health and Human Development |
| 4551 | NNT | Number Needed to Treat |
| 4552 | NVK | Dutch Society of Pediatricians; in Dutch: Nederlandse Vereniging voor |
| 4553 | | Kindergeneeskunde |
| 4554 | PDA | Persistent Ductus Arteriosus |
| 4555 | PMA | PostMenstrual Age |
| 4556 | PNA | PostNatal Age |
| 4557 | PVL | PeriVentricular Leucomalacia |
| 4558 | RCT | Randomised Controlled Trial |
| 4559 | RI | Respiratory Index |
| 4560 | SAE | Serious Adverse Event |
| 4561 | SD | Standard Deviation |
| 4562 | Sponsor | The sponsor is the party that commissions the organisation of |
| 4563 | | performance of the research, for example a pharmaceutical company, |
| 4564 | | academic hospital, scientific organisation or investigator. A party that |
| 4565 | | provides funding for a study but does not commission it is not |
| 4566 | | regarded as the sponsor, but referred to as a subsidising party. |
| 4567 | VLBW | Very Low Birth Weight |
| 4568 | WMO | Medical Research Involving Human Subjects Act; in Dutch: Wet |
| 4569 | | Medisch-wetenschappelijk Onderzoek met Mensen |

4570

4571

4572 **SUMMARY**

4573 **Background:** Randomised controlled trials (RCTs) have shown that treatment of chronically
4574 ventilated preterm infants after the first week of life with dexamethasone reduces the
4575 incidence of bronchopulmonary dysplasia (BPD). However, there are concerns that its use
4576 may increase the risk of adverse neurodevelopmental outcome. Hydrocortisone has been
4577 suggested as an alternative therapy. So far no RCT has investigated its efficacy when
4578 administered after the first week of life to ventilated preterm infants.

4579 **Objective:** To establish the efficacy of hydrocortisone given after one week of life to reduce
4580 the incidence of the combined outcome death or BPD in chronically ventilated preterm
4581 infants.

4582 **Study design:** Randomised double blind placebo controlled multicenter study.

4583 **Study population:** Very low birth weight infants (GA<30weeks and/or BW<1250grams),
4584 ventilator dependent at a postnatal age of 7 – 14 days.

4585 **Intervention:** Administration of hydrocortisone or placebo during a 22 day tapering
4586 schedule.

4587 **Outcome parameters:** Primary outcome measure is survival free of BPD at 36 weeks
4588 postmenstrual age (PMA). Secondary outcomes are short term effects on the pulmonary
4589 condition, adverse effects during hospitalization, and long-term neurodevelopmental
4590 sequelae assessed at 2 years corrected gestational age (CGA).

4591 **Burden, benefit and risks associated with participation; group relatedness:**

4592 Burden: All infants participating in (either treatment arm of) the study are subjected to
4593 routine neonatal intensive care. The administration of the study intervention itself
4594 (hydrocortisone or placebo administration) does not pose an extra burden on the patients.
4595 This study does not require extra investigations or interventions.

4596 Benefit and risks: Hydrocortisone may facilitate extubation and thereby reduce the total
4597 duration of mechanical ventilation. In addition, hydrocortisone may reduce the incidence of
4598 BPD. Both these beneficial effects may improve neurodevelopmental outcome. On the other
4599 hand, use of hydrocortisone may increase the risk for hyperglycaemia, hypertension,
4600 systemic infection, gastrointestinal perforation and a delay in neurodevelopment. However,
4601 gastrointestinal perforation and delayed neurodevelopment have only been reported in
4602 studies administering corticosteroids in the first week of life and/or during combinations
4603 with other medication. In this study the risk of gastrointestinal perforation and delayed
4604 neurodevelopment may be reduced because hydrocortisone will be administered after the
4605 first week of life and combinations with other drugs will be avoided as much as possible.
4606 Infants assigned to the placebo group will not benefit from the aforementioned possible
4607 beneficial effects nor be subjected to the possible adverse effect of hydrocortisone.

4608 Group relatedness: BPD is a complication occurring exclusively in preterm infants. Any
4609 intervention aiming to reduce the risk of this complication therefore needs to be studied in
4610 this specific population at risk.

4611 **1. BACKGROUND**

4612 Bronchopulmonary dysplasia (BPD) is the most common complication of premature birth,
4613 with a reported incidence of 8% to 35%.^{1,2} BPD is characterized by chronic respiratory
4614 distress, the need for prolonged respiratory support, an increased risk of recurrent
4615 pulmonary infections, airway hyperreactivity during the first years of life³ and life-long
4616 alterations in lung function.⁴⁻⁶ Patients with established BPD have high rates of readmissions
4617 and utilization of health services resulting in tremendous societal costs compared to children
4618 without BPD.⁷⁻⁹ Furthermore, BPD is considered an important risk factor for adverse
4619 neurodevelopmental outcome after premature birth¹⁰⁻¹⁴ with life-long economic and social
4620 consequences.¹⁵⁻¹⁸

4621

4622 In addition to direct mechanical injury, caused by artificial ventilation and oxygen toxicity,
4623 pulmonary inflammation has been identified as an important mediator in the development
4624 of BPD.¹⁹⁻²¹ This is the rationale for treating patients with glucocorticoids, a well known anti-
4625 inflammatory agent. Randomised controlled trials (RCTs) summarized in several systematic
4626 reviews have shown that postnatal systemic glucocorticoids, mainly dexamethasone, reduce
4627 the risk of the combined outcome death or BPD in ventilated preterm infants.²²⁻²⁴

4628 Furthermore, systemic glucocorticoids seem to be most effective when administered in a
4629 time frame of 7 to 14 days postnatal age, the so-called moderately early treatment
4630 onset.^{25,26} However, initiating dexamethasone treatment in the first days of life seems to be
4631 associated with an increased the risk of cerebral palsy (CP). Although this complication has
4632 not been reported by RCTs investigating dexamethasone treatment initiated after the first
4633 week of life, these alarming reports have resulted in a general concern on the use of
4634 dexamethasone in preterm infants.²⁷⁻²⁹ Based on this concern, the American Academy of

4635 Pediatrics, Canadian Paediatric Society, and the European Association of Perinatal Medicine
4636 have stated that clinical trials should be performed to investigate the use of alternative anti-
4637 inflammatory glucocorticoids, such as the less potent glucocorticoid hydrocortisone.^{30,31}
4638
4639 Despite the ongoing concerns on their use, systemic glucocorticoids are still used in
4640 approximately 10% of the preterm infants at risk for BPD.³²⁻³⁴ Dexamethasone is still the
4641 most widely used glucocorticoid drug, but its dose has been significantly reduced and
4642 administration is often postponed until the 3rd or 4th week of life.²⁷
4643
4644 As an alternative, many clinicians have started to use hydrocortisone. Animal data suggest
4645 that hydrocortisone has a less detrimental effect on the brain than dexamethasone.³⁵
4646 However, no placebo controlled RCT has investigated the use of hydrocortisone after the
4647 first week in life in ventilator dependent preterm infants.³⁶ Six RCTs investigating a low
4648 hydrocortisone dose started within < 72 hours after birth (early treatment) failed to show a
4649 clear reduction in the incidence of BPD.³⁷⁻⁴² Only one of these trials reported long-term
4650 follow-up, showing no differences in adverse neurodevelopmental sequelae.⁴³ These
4651 findings are supported by several historical cohort studies, showing no increased risk of
4652 adverse neurodevelopmental outcome in hydrocortisone treated infants.⁴⁴⁻⁴⁶
4653
4654 In most Dutch Neonatal Intensive Care Units (NICUs) preterm infants who are ventilator-
4655 dependent in the second week of life are no longer treated with glucocorticoids. Infants are
4656 kept on the ventilator allowing spontaneous recovery of lung function over time, sometimes
4657 supported by other interventions, such as diuretics and inhalation therapy. With this
4658 approach, some infants can be successfully weaned and extubated. Only those infants that

4659 remain ventilator dependent after 3-4 weeks are treated with glucocorticoids, with the
4660 primary objective to wean and extubate.

4661 Although this approach will undoubtedly result in successful extubation of most infants with
4662 the lowest possible use of glucocorticoids, the question remains if this is also the best
4663 strategy in reducing the incidence of BPD in preterm infants ventilated after 7 days of life.
4664 This question seems justified and relevant because BPD, and not failure to extubate, is
4665 associated with adverse medium- and long-term outcome. This is the main reason why the
4666 primary outcome of this study is death or BPD and not failure to extubate.

4667

4668 The NICU at the University Medical Center Utrecht has historically used hydrocortisone for
4669 chronically ventilated preterm infants. Retrospective studies seem to indicate that
4670 hydrocortisone is effective in reducing BPD, without causing serious adverse effects.
4671 However, these findings need to be confirmed or refuted by a large randomized placebo
4672 controlled trial. Despite the absence of randomized evidence, three out of the 10 Dutch
4673 NICUs switched from dexamethasone to hydrocortisone. This diversity in treatment between
4674 NICUs is undesirable and has also been debated in the public press.⁴⁷ As a first step to
4675 resolve this diversity in treatment, all 10 Dutch NICUs have indicated that a RCT comparing
4676 hydrocortisone with placebo is urgently needed, an initiative that is also supported by the
4677 Dutch Society of Pediatricians (NVK), giving such a trial top priority. Since the NICUs which
4678 already use hydrocortisone are reluctant or refuse to prescribe dexamethasone as trial
4679 medication, a RCT comparing dexamethasone versus hydrocortisone is not possible.

4680

4681 The optimal dose of hydrocortisone is currently unknown. However, the NICU in Utrecht has
4682 been using a fixed hydrocortisone treatment regimen for several decades now and this

4683 regimen has also been adopted by the other Dutch NICUs using hydrocortisone.
4684 Retrospective studies strongly suggest that this is a safe dose, because it was not associated
4685 with an increased risk of adverse neurological outcome.^{45,48} Comparing hydrocortisone
4686 treated patients with dexamethasone treated patients in other NICUs showed no difference
4687 in the incidence of BPD, suggesting that this dose is equally effective in reducing BPD.⁴⁸
4688 Based on these findings and current clinical practice, we decided to adopt the dosing
4689 regimen from Utrecht for this study.

4690

4691 Based on the current available evidence, the American Academy of Pediatrics has concluded
4692 that: (1) routine use of systemic dexamethasone for the prevention or treatment of CLD in
4693 infants with VLBW is not recommended; (2) outside the context of a randomized, controlled
4694 trial, the use of corticosteroids should be limited to exceptional clinical circumstances. Based
4695 on these recommendation ventilated preterm infants are no longer routinely treated with
4696 postnatal corticosteroids. Furthermore, in exceptional cases treatment is, in most cases,
4697 postponed until after the third week of life. Comparison of hydrocortisone to a placebo is
4698 therefore warranted because standard therapy in the second week of life (7-14 d after birth)
4699 is to wait for spontaneous recovery of lung function. In exceptional clinical circumstances
4700 treatment with a (rescue) open label glucocorticoids is still possible in the current study.

4701 Although based on the above, the *extra* risks for the patients in this study are probably
4702 limited, a data monitoring committee will closely monitor any possible adverse effects and
4703 risks, as also explained in paragraph 9.4.

4704

4705 **2. OBJECTIVE**

4706 To investigate if hydrocortisone is safe and effective in reducing the incidence of the
4707 combined outcome death or BPD at 36 weeks PMA in chronically ventilated preterm infants,
4708 as compared to placebo. This study **does not** aim to successfully extubate ventilator-
4709 dependent preterm infants with the lowest possible use of glucocorticoids (i.e.
4710 hydrocortisone), but to use glucocorticoids as an early intervention (7-14 d after birth) to
4711 reduce the risk of death or BPD in these ventilator-dependent preterm infants. From this
4712 point of view the treatment strategy is fundamentally different from what is currently used
4713 in daily clinical practice.

4714

4715 **3. STUDY DESIGN**

4716 Multicenter randomised double-blind placebo-controlled trial with a total duration of 5 years
4717 conducted in 15 neonatal intensive care units in the Netherlands (n=10) and Belgium (n=5).

4718

4719 **4. STUDY POPULATION**

4720 **4.1 Population eligibility**

4721 Ventilated VLBW infants at high risk for BPD treated in a level III NICU

4722

4723 **4.2 Inclusion criteria**

4724 Preterm infants with an increased risk of BPD and:

- 4725 - a gestational age < 30 wks and/or birth weight < 1250 g
- 4726 - ventilator dependency at 7-14 days PNA
- 4727 - *a respiratory index* ($RI = MAwP \times FiO_2$) of ≥ 2.5 for more than 12 h/day for at least
4728 48 hours, ensuring adequate oxygen saturation (85-95%) and pCO₂ values in
4729 premature infants (5.0-7.5 kPa).

4730 Note: these targets are used to ensure homogeneous assessment of MAwP and FiO₂ for
4731 patient inclusion among participating centres. For the same reason, clinician are
4732 encouraged to aim for the median value of these targets when assessing the RI. After
4733 inclusion of the patient in the study, physicians are free to use local targets for
4734 oxygenation and ventilation.

4735

4736 **4.3 Exclusion criteria**

4737 - chromosomal defects (e.g. trisomy 13, 18, 21)

4738 - major **congenital** malformations that:

4739 ○ compromise lung function (e.g. surfactant protein deficiencies, congenital

4740 diaphragmatic hernia)

4741 ○ result in chronic ventilation (e.g. Pierre Robin sequence)

4742 ○ increase the risk of death or adverse neurodevelopmental outcome

4743 (congenital cerebral malformations)

4744 Note: intraventricular haemorrhages, periventricular leucomalacia and

4745 cerebral infarction are not considered **congenital** malformations and

4746 therefore are no exclusion criteria.

4747 - Use of dexamethasone or hydrocortisone for the sole purpose of improving lung

4748 function and respiratory status prior to inclusion

4749

4750 Considerations

4751 Although (suspected or proven) sepsis, pneumonia, necrotizing enterocolitis (NEC) and

4752 patent ductus arteriosus (PDA) are well-known causes of respiratory failure, these diagnoses

4753 are known to be independent risk factors for developing BPD. Therefore, these diagnoses are
4754 **not** considered to be exclusion criteria. The following should be taken into consideration:

4755 13. In ventilator-dependent cases of sepsis and pneumonia the attending physician may
4756 start antibiotics and await the effect on respiratory drive/ pulmonary status for 48
4757 hours. If the patient meets the inclusion criteria after 48 h, he/she is eligible for
4758 inclusion.

4759 14. Trials studying the early use (initiated < 96 hours after birth) of corticosteroids have
4760 shown that treatment with corticosteroids may increase the risk of intestinal
4761 perforation. Speculating on the pathogenesis of this adverse effect, it has been
4762 suggested that the synchronous use of indomethacin and corticosteroids might
4763 explain this finding. However, trials starting dexamethasone between 7-14 d after life
4764 have **not** reported an increased risk of intestinal perforation, despite the fact that
4765 some of these patients were also treated for hemodynamically significant PDA with
4766 indomethacin. In other words, the evidence for a possible adverse effect of the
4767 combined use of corticosteroids and indomethacin/ibuprofen is weak. For this reason
4768 the combined use of corticosteroids and indomethacin/ibuprofen is **NOT** prohibited
4769 within the STOP-BPD trial. However, where possible in the time window of 7-14 days,
4770 we do encourage physicians to treat a hemodynamically significant PDA before
4771 randomizing the patient for the study. To make this feasible physicians are strongly
4772 encouraged to determine the presence of a hemodynamically significant PDA at day
4773 7 of life. This way the patient can, if necessary according to the local protocol, still be
4774 treated with 2 courses of indomethacin / ibuprofen before day 14 of life.
4775 If there is an indication to treat a hemodynamically significant PDA with
4776 indomethacin/ibuprofen after randomization, study medication is **NOT** stopped. Yet,

4777 any synchronous use of indomethacin/ibuprofen and study medication or the
4778 occurrence of an intestinal perforation recorded in the case record form, will
4779 automatically result in so-called **Alert Procedure** (see paragraph 9.4. Such an **Alert**
4780 **Procedure**. This will allow for a close and individual monitoring of possible adverse
4781 effects.

4782 15. If the physician considers extubation not an option because of the general condition
4783 of the infant (e.g. NEC with severe hemodynamic instability and severe abdominal
4784 distension) inclusion in the study can be postponed until the maximum of 14 days
4785 PNA.

4786

4787 **4.4 Sample size calculation**The primary outcome parameter is BPD free survival at 36 weeks
4788 PMA. The a priori risk of death or BPD in preterm infants less than 30 weeks gestation and
4789 ventilated in the second week of life is estimated at 60 – 70%. The meta-analysis on
4790 moderately early dexamethasone treatment estimated an absolute risk reduction (ARR) of
4791 25% (NNT=4) compared with placebo.²⁴ However, there are no data currently available on
4792 the efficacy of hydrocortisone and the suggested cumulative dose in the present study is
4793 considerably lower compared to previously used dexamethasone doses. Since the shown
4794 efficacy of dexamethasone is dependent on the used doses in these trials²⁶, we would
4795 propose a more conservative approach, defining an ARR of 15% or more (NNT=7) as clinically
4796 relevant. With an estimated a priori risk for death or BPD at 36 weeks PMA of 60%, a type I
4797 error of 5% (2 tailed) and a power of 80% the number of patients to be included in each
4798 treatment arm would be 175 (total 350). Anticipating a 10% drop out of randomized
4799 patients, 200 patients need to be included in each treatment arm (total 400). Based on a
4800 retrospective analysis of ventilated preterm infants at day 7 of life in the majority of Dutch

4801 NICUs we expect a total of 200 eligible patients each year. With an estimated inclusion rate
4802 of 66% of eligible patients and an inclusion period of 3 years, a total of 400 patients should
4803 be included in the study. For sample size calculation we used Nquery (Statistical Solutions
4804 Ltd., Cork, Ireland).

4805

4806 **5. TREATMENT OF SUBJECTS**

4807 **5.1. Therapeutic details**

4808 5.1.1 Preparation of the trial medication: The infants of the hydrocortisone group will receive
4809 hemisuccinate hydrocortisone 5mg/kg/day Q.I.D for 7 days, followed by 3.75 mg/kg/day
4810 T.I.D. for 5 days, subsequently lowering the frequency by one dose every 5 day. This leads to
4811 a total duration of therapy of 22 days and a cumulative dose of 72.5 mg/kg hydrocortisone
4812 (see appendix 1). The infants in the control group receive saline placebo for the entire 22-day
4813 period in the same frequency as the hydrocortisone group. Both saline and hydrocortisone
4814 schedules will be calculated according to weight on the day of randomisation and not adjusted
4815 to the actual weight during the tapering schedule. Clinicians are encouraged to administer the
4816 study medication intravenously as long as this route of access is required for other reasons. If
4817 intravenous access is no longer required for the standard treatment, the study medication can
4818 be administered orally using the same solution and dose.

4819

4820 5.1.2 Adjusting study medication for transient short-term adverse effects: previous studies on
4821 corticosteroids use in the second week of life (mainly dexamethasone) have reported that the
4822 following transient short term side-effects: hyperglycaemia, increased risk of infection, and
4823 hypertension. Hyperglycaemia and infection occur frequently at the NICU as co-morbidity of
4824 preterm birth and its treatment. There is extensive experience in treating these morbidities
4825 with, respectively, insulin and antibiotics. Although the incidence of hyperglycaemia and/or

4826 infection will be closely monitored (secondary endpoints), in case of an event, the study
4827 medication should **NOT** be adjusted.
4828 Hypertension is a much less common morbidity after preterm delivery and antihypertensive
4829 drugs are not routinely used in neonatal care. Corticosteroids induced hypertension is usually
4830 treated and resolved by reducing the dose. So, in case of hypertension, the study medication is
4831 lowered according to appendix 1 if no other treatable cause of hypertension can be identified.
4832 Hypertension is defined as a **systolic** blood pressure > 80 mmHg for infants 24-26 wks, > 90
4833 mmHg for infants 26-28 wks, and > 100 mmHg for infants \geq 28 wks. Data on the time, reason
4834 and dose adjustment will be collected. The presence of hypertension leading to adjustment of
4835 study medication will be reported via the **Alert Procedure** (see paragraph 9.4).

4836

4837 5.1.3 Stop criteria during study protocol medication (treatment failure): In general,
4838 the use of open label hydrocortisone during the 22 day treatment course is strongly
4839 discouraged. Open label hydrocortisone use **may be considered** in the following conditions:

- 4840 5. The pulmonary condition is progressively deteriorating and the respiratory index
4841 (MAwP x FiO₂) is > 10 for more than 6 consecutive hours.
- 4842 6. The pulmonary condition of the patient is stable (RI < 10) but not improving over
4843 time. In these circumstances open label hydrocortisone **may be considered** if the
4844 following conditions are met:
- 4845 a. Extubation was attempted (extubation trial) within 24 hours before considering
4846 open label treatment and this attempt failed.
 - 4847 b. The patient is on study medication for **at least** 10 days (but preferably at a later
4848 time).

4849 The open label hydrocortisone dosage schedule is similar to that used in the study. At that
4850 point in time the study medication is stopped and the patient will be recorded as “treatment

4851 failure". In case of treatment failure the following data will be collected: timing of treatment
4852 failure, ventilator support and settings, type of open label medication, starting date,
4853 cumulative dose and duration of rescue therapy. The patients will be followed as all other
4854 patients until the clinical endpoints occur or until end of follow up.

4855 **The use of open label hydrocortisone will be reported via the Alert Procedure** (see
4856 paragraph 9.4).

4857

4858 5.1.4 Late rescue therapy outside study protocol (late rescue glucocorticoids): Patients still on
4859 mechanical ventilation after completion of the study medication, i.e. day 22, may be treated
4860 with open label hydrocortisone. In such cases the physician should first attempt extubation
4861 before considering open label use. The open label hydrocortisone dosage schedule is similar
4862 to that used in the study (see appendix 1). Data on the starting date, cumulative dose and
4863 duration of rescue therapy are collected.

4864

4865 5.1.5 Anti-hypotensive therapy: In case of persistent hypotension, not (sufficiently)
4866 responding to first line treatment with intravascular volume expansion and inotropes
4867 (dopamine and/or dobutamine) the use of hydrocortisone is allowed in a dose of 3 mg/kg/day
4868 for 5 days. Treatment for hypotension will not be considered as treatment failure. Data on
4869 timing, dose and duration will be collected.

4870

4871 5.1.6 Stress dosing during and after study medication: Infants treated for a longer period of
4872 time with corticosteroids might experience inadequate adrenal response to stress (i.e. surgery
4873 or sepsis) for several months after stopping treatment. For this reason corticosteroids
4874 treatment is almost always tapered over time, as this minimizes the risk of adrenal
4875 insufficiency. Some NICUs consider this risk to be so low, that they will only treat patients

4876 with corticosteroids if they show signs of adrenal insufficiency (hypotension,
4877 hypoglycaemia), while other NICUs will start **preventive** treatment with corticosteroids in
4878 case of stressful events such as surgery. This study will also allow for a **preventive** stress
4879 dose treatment if this is deemed necessary according to the local protocol of the participating
4880 NICU. In other words, **preventive** treatment with a stress dose is **NOT** mandatory.
4881 It is clear that only the patients receiving hydrocortisone, and not those allocated to placebo
4882 treatment, will potentially benefit from a stress dose of hydrocortisone. For this reason
4883 patients will receive a stress dose identical to their study medication. A separate, second
4884 (stress) randomization procedure will make sure that allocation occurs in a blinded fashion.
4885 When the event occurs after completion of study medication, the prescribed dosing schedule
4886 is 5 mg/kg Q.I.D. on the day the event occurs, subsequently lowering the frequency by one
4887 dose every day. This leads to a total duration of stress dosing therapy of 5 days and a
4888 cumulative dose of 15 mg/kg study medication. In case the stress event occurs during study
4889 treatment, a stress dose is only started after the first week of treatment. In that case the actual
4890 dose is increased to 5 mg/kg Q.I.D. and subsequently lowered according to the
4891 aforementioned stress schedule until the actual dose of study medication is once again
4892 reached. From that point onwards the original regimen of study medication will be followed
4893 again.
4894 It is important to emphasize that the above mentioned procedure only applies to **preventive**
4895 treatment in case of a stressful event. If a patients shows signs of adrenal insufficiency at any
4896 time during a stressful events, he or she should be treated with open label hydrocortisone
4897 according to the dosing schedule mentioned in this paragraph.
4898 Data on number of courses, timing and dose will be collected.
4899

4900 5.1.7 Inhalation corticosteroids: There is currently insufficient evidence that inhaled
4901 corticosteroids will reduce the risk of death or BPD in preterm infants. Use of inhaled
4902 corticosteroids in the first weeks of life is therefore strongly discouraged. However, its use is
4903 not an exclusion criterion. Data on timing, dose and duration will be collected.

4904

4905 **5.2. Use of co-intervention**

4906 All randomized patients will be treated according to the guidelines of the individual NICUs.
4907 All participating NICUs explore treatable causes of ventilator dependency during the first
4908 week of life, such as patent ductus arteriosus, sepsis and pneumonia as much as possible and
4909 treat these according to the department protocol. Although all of these conditions can be an
4910 alternative cause of respiratory failure, they are known risk factors for developing BPD and
4911 therefore are not considered exclusion criteria.

4912

4913 This trial will monitor the prognostic important co-interventions and conditions, as described
4914 in section 8.2.

4915

4916 **6. INVESTIGATIONAL MEDICINAL PRODUCT**

4917 **6.1 Name and description of investigational medicinal product**

4918 In this multicenter study the investigational medicinal product is hydrocortisone. A detailed
4919 description of hydrocortisone can be found in the summary of product characteristics (SPC)
4920 which is added to this protocol as a separate document.

4921

4922 **6.2 Summary of findings from non-clinical studies**

4923 More details on both hydrocortisone and the placebo used in this study can be found in,
4924 respectively, the summary of product characteristics (SPC) and investigational medicinal
4925 product dossier (IMPD) both added to this protocol as separate documents. In addition to
4926 this information, animal studies have shown that hydrocortisone, in contrast to
4927 dexamethasone, did not increase the risk of adverse effects on the brain when compared to
4928 a placebo.³⁵

4929

4930 **6.3 Summary of findings from clinical studies**

4931 Hydrocortisone has several authorized indications as listed in the SPC on page 1. In preterm
4932 infants, hydrocortisone is used for the following indications: 1) primary or secondary
4933 deficiency of corticosteroids; 2) treatment of hypotension; and 3) anti-inflammatory drug in
4934 developing bronchopulmonary dysplasia (BPD). According to the SPC (page 1) only the first
4935 indication is authorized. The fact that hydrocortisone is used for other unauthorized
4936 indications is not exceptional, because off-label use of medication is more the rule than the
4937 exception in neonatology. In this study, hydrocortisone is used for its anti-inflammatory
4938 properties on the lungs of preterm infants at high risk for BPD ventilated in the second week

4939 of life, aiming to reduce the incidence of BPD. To date, six RCTs investigating a low
4940 hydrocortisone dose started within < 72 hours after birth (early treatment) failed to show a
4941 clear reduction in the incidence of BPD.³⁷⁻⁴² Only one of these trials reported long-term
4942 follow-up, showing no differences in adverse neurodevelopmental sequelae.⁴³ Use of
4943 hydrocortisone after the first week of life with a higher dose has been the standard of care in
4944 4 of the 10 Dutch NICUs. The University Medical Center Utrecht has used hydrocortisone in
4945 an identical treatment schedule as this study for several decades. Several historical cohort
4946 studies have shown that hydrocortisone use for this indication (reduction of BPD) did not
4947 increase the risk of adverse neurodevelopmental outcome.⁴⁴⁻⁴⁶

4948

4949 **6.4 Summary of known and potential risks and benefits**

4950 As studies with hydrocortisone are limited, the assessment of risks and benefits are based on
4951 data obtained from previous RCTs investigating other corticosteroids (mainly
4952 dexamethasone) in ventilated preterm infants at risk for BPD. Based on these studies,
4953 hydrocortisone may facilitate extubation and thereby reduce the total duration of
4954 mechanical ventilation. In addition, hydrocortisone may reduce the incidence of BPD. Both
4955 these beneficial effects may improve neurodevelopmental outcome. On the other hand, use
4956 of hydrocortisone may increase the risk for hyperglycaemia, hypertension, systemic
4957 infection, gastrointestinal perforation and a delay in neurodevelopment. However,
4958 gastrointestinal perforation and delayed neurodevelopment have only been reported in
4959 studies administering corticosteroids in the first week of life and/or during combinations
4960 with other medication. In this study the risk of gastrointestinal perforation and delayed
4961 neurodevelopment may be reduced because hydrocortisone will be administered after the
4962 first week of life and combinations with other drugs will be avoided as much as possible.

4963 Infants assigned to the placebo group will not benefit from the aforementioned possible
4964 beneficial effects nor be subjected to the possible adverse effect of hydrocortisone.

4965

4966 **6.5 Description and justification of route of administration and dosage**

4967 The optimal dose of hydrocortisone is currently unknown. However, the NICU in Utrecht has
4968 been using a fixed hydrocortisone treatment regimen for several decades now and this
4969 regimen has also been adopted by the other Dutch NICUs using hydrocortisone.

4970 Retrospective studies strongly suggest that this is a safe dose, because it was not associated
4971 with an increased risk of adverse neurological outcome.^{45,48} Comparing hydrocortisone
4972 treated patients with dexamethasone treated patients in other NICUs showed no difference
4973 in the incidence of BPD, suggesting that this dose is equally effective in reducing BPD.⁴⁸

4974 Based on these findings and current clinical practice, we decided to adopt the dosing
4975 regimen from Utrecht for this study. More details on the dose regiment and the route of
4976 administration can be found in paragraph 5.1.

4977

4978 **6.6 Preparation and labelling of Investigational Medicinal Product**

4979 Preparation and labelling will be done according to relevant GMP guidelines. Hydrocortisone
4980 (Pharmachemie BV Holland) will be provided via the AMC pharmacy (Dr. M. Kemper) and the
4981 placebo will be manufactured by ACE Pharmaceuticals BV (Zeevolde, the Netherlands). The
4982 SPC of hydrocortisone and the IMPD of the placebo are provided as separate documents. In
4983 addition, we have added an example of labels for the vials and boxes as separate
4984 documents.

4985

4986 **6.7 Drug accountability**

4987 Drug accountability will be according to current GMP guidelines. The “kenniscentrum
4988 geneesmiddelen onderzoek” of the AMC pharmacy will take full responsibility and
4989 supervision of the drug accountability process.

4990

4991 **7. METHODS**

4992 **7.1 Randomisation, blinding and treatment allocation**

4993 Written informed consent has to be obtained from either parents or care-givers prior to
4994 randomisation. In case of ventilator dependency after day 7 of life with a suspected diagnosis
4995 of developing BPD, parents receive the study information as soon as possible allowing them
4996 sufficient time to consider participation. The actual decision to include the patient in the trial
4997 should be made between day 7 and 14 PNA. Following inclusion and randomization, the first
4998 dose of study medication should be administered within 24 hours. Randomization will be
4999 centrally controlled and web-based using a computer program designed for this study. This
5000 trial will be protected from selection bias by using concealed, stratified and blocked
5001 randomisation.

5002

5003 Randomisation will be per center and stratified according to gestational age stratum (Stratum
5004 A: < 27 weeks; Stratum B: \geq 27 weeks), in order to achieve an equal distribution in both
5005 treatment arms. The allocation ratio will be 1:1 with block randomisation using variable block
5006 sizes. Multiple birth infants will be randomised independently, unless the parents or
5007 caretakers explicitly demand that the siblings should be treated according to the same
5008 treatment arm. An automated mechanism to perform twin randomisation is in place.

5009 The infants' parents and all members of the medical team, including investigators, remain
5010 blinded to group assignment throughout the study.

5011

5012 Patient characteristics, including gestational age, birth weight and respiratory status, will be
5013 collected from all eligible infants that are not included in the study. In addition, we will
5014 collect data on why the patients were not included. With this information we will assess
5015 possible bias in patient inclusion.

5016

5017 **7.2 Withdrawal of individual subjects**

5018 Parents or caregivers can leave the study at any time for any reason if they wish to do so
5019 without any consequences.

5020 Note: patients who are considered to have "treatment failure" based on the prespecified
5021 criteria (paragraph 5.1.3) are **NOT** withdrawn from the study, and remain in follow up.

5022

5023 **7.3 Replacement of individual subjects after withdrawal**

5024 The number of withdrawn patients not marked as prespecified treatment failure (see section
5025 7.2) will be replaced.

5026

5027 **7.4 Follow-up of subjects withdrawn from treatment**

5028 Subjects withdrawn from the study will be treated according to the standard of care, including
5029 neurodevelopmental outcome assessment at the outpatient clinic.

5030

5031 **7.5 Premature termination of the trial**

5032 An independent Data Monitoring Committee (DMC) will monitor the study on safety aspects
5033 (see section 9.4) and if necessary recommend termination of the study.

5034

5035 **7.6 Breaking the randomization code**

5036 Unblinding is only performed in emergency situations where knowledge of the identity of the
5037 study drug is considered absolutely necessary for the clinical management of the subject. If
5038 local investigator or attending physician decides unblinding is essential, (s)he will make every
5039 effort to contact the PI before unblinding to discuss options. For this purpose a 24/7 reachable
5040 telephone service will be installed. Details of the unblinding procedure will be defined in the
5041 study specific working instructions.

5042

5043 **7.7. Endpoints**

5044 7.7.1. Primary endpoint: the dichotomous variable BPD free survival at 36 weeks PMA. BPD
5045 at 36 weeks PMA will be assessed according to the NIHCHD Consensus Statement defining
5046 normal oxygen saturation as 86%-94%. The severity of the BPD will be assessed as proposed
5047 by Jobe et.al.²¹, since the severity of BPD has a high association with neurodevelopmental
5048 sequelae.¹² In case of supplemental oxygen delivery >21% and < 30% or low flow at 36 weeks
5049 PMA, the oxygen reduction test as described by Walsh et.al.^{21,49,50} should be preformed. A
5050 positive oxygen reduction test has a high correlation with the risk on discharge home with
5051 oxygen, the length of hospital stay, and pulmonary morbidity requiring hospital readmission
5052 during the first year of life. For practical guidance on the use of the oxygen reduction test
5053 please go to appendix 2.

5054

5055 7.7.2. Secondary endpoints:

- 5056
- treatment failure as defined in section 5.1.3
- 5057
- mortality at 28 days PNA, 36 weeks PMA and at hospital discharge

- 5058 • BPD at 28 days
- 5059 • failure to extubate 3, 7, 14 and 21 days after initiating therapy
- 5060 • duration of mechanical ventilation
- 5061 • use of “rescue treatment” with hydrocortisone outside the study protocol
- 5062 • total time on supplemental oxygen
- 5063 • length of hospital stay
- 5064 • incidence of hypertension, as defined in paragraph 5.1.2
- 5065 • hyperglycaemia requiring the use of insulin therapy
- 5066 • nosocomial infection, like sepsis, meningitis and pneumonia
- 5067 • pulmonary hemorrhage, pneumothorax and pulmonary interstitial emphysema
- 5068 • hemodynamic significant patent ductus arteriosus for which medical intervention or
- 5069 surgical ligation is needed
- 5070 • necrotising enterocolitis (NEC), diagnosed at surgery, autopsy or by radiographic
- 5071 finding of pneumatosis intestinalis or hepatobiliary gas (Bell stage II)
- 5072 • gastrointestinal bleeding
- 5073 • isolated gastrointestinal perforation diagnosed on abdominal radiography
- 5074 • intraventricular haemorrhage (IVH) and/or periventricular leucomalacia (PVL),
- 5075 including grading on cerebral ultrasonography according to protocol defined by Ment
- 5076 et.al.⁵¹
- 5077 • retinopathy of prematurity, including grading following international classification⁵²
- 5078 • weight, head circumference and length at 36 weeks PMA
- 5079 • long-term health and neurodevelopmental sequelae, assessed at 2 years c.a.:
- 5080 ○ readmissions since first discharge home
- 5081 ○ weight, length and head circumference at 24 months c.a.

- 5082 ○ Bayley Scales of Infant Development III, Mental Developmental Index and
- 5083 Psychomotor Developmental Index
- 5084 ○ cerebral palsy and severity of cerebral palsy using gross motor function
- 5085 classification system
- 5086 ○ hearing loss requiring hearing aids
- 5087 ○ blindness
- 5088 ○ behavioural problems (child behaviour checklist)

5089

5090 All primary and secondary endpoints are measured as part of standard usual care in the
5091 Netherlands and Belgium, and will be derived from the charts of the patients by the
5092 investigators.

5093 **8. DATA COLLECTION AND STATISTICAL ANALYSIS**

5094 **8.1 Baseline characteristics**

5095 Baseline characteristics are collected prior to inclusion and randomization with respect to the
5096 following baseline characteristics: demographic details and patient characteristics, such as
5097 gestational age, small for gestational age, antenatal problems, antenatal steroids, surfactant
5098 therapy, mode of delivery, resuscitation details, Apgar scores, presence of IVH/PVL, and
5099 occurrence of PDA. Base line characteristics on ventilator settings, gas exchange will be
5100 collected on day of randomization.

5101

5102 **8.2 Co-interventions**

5103 Apart from the study medication all patients will receive standard care, including co-
5104 medication such as surfactant, inhaled nitric oxide. methylxanthines, vitamin A, antibiotics,
5105 antimycotic therapy, diuretics, ibuprofen/indomethacine, inotropes, and inhaled
5106 corticosteroids. These co-medications are prescribed on the basis of (inter)national guidelines

5107 and/or local protocols. Since the route of administration (e.g. oral or IV), the dose and
5108 frequency may vary continuously depending on the weight and the clinical condition of the
5109 patients, only name, start and stop date are recorded in the CRF. For all other drugs used
5110 during the admission data will be recorded according to GCP guidelines.

5111 Also the ventilation mode with the ventilator settings will be recorded and analyzed.

5112

5113 **8.3 Statistical analysis**

5114 Normally distributed data will be presented as mean \pm standard deviations, not-normally
5115 distributed data as medians and (interquartile) ranges. Categorical data will be analysed
5116 using the Chi-square test. Continuous data will be analysed using the Student's *t* test or
5117 Mann-Whitney test as appropriate. Both intention-to-treat and per-protocol analysis will be
5118 employed. The effect of hydrocortisone on the primary outcome death or BPD will be
5119 assessed by multi-variable logistic regression analysis including possible confounders.
5120 Statistical significance is set at $p < 0.05$.

5121

5122 **9. SAFETY REPORTING**

5123 **9.1 Section 10 WMO (Wet Medisch-wetenschappelijk Onderzoek met Mensen)**

5124 In accordance with section 10, subsection 1, of the Dutch WMO, the investigator will inform
5125 the subjects' parents or caregivers and the reviewing accredited METC (*Medisch Ethische*
5126 *Toetsingscommissie*) if anything occurs, on the basis of which it appears that the
5127 disadvantages of participation may be significantly greater than was foreseen in the research
5128 proposal. The study will be suspended pending further review by the accredited METC,
5129 except insofar as suspension would jeopardise the subjects' health. The investigator will
5130 ensure that all subjects' parents or caregivers are kept informed.

5131

5132 **9.2 Adverse and serious adverse events (SAE)**

5133 Adverse events are defined as any undesirable experience occurring to a subject during a
5134 clinical trial, whether or not considered related to the investigational drug. All adverse
5135 events observed by the investigator or his staff will be recorded. A **serious adverse event** is
5136 any untoward medical occurrence or effect that at any dose

5137 - results in death;

5138 - is life threatening (at the time of the event);

5139 - requires hospitalization or prolongation of existing inpatients' hospitalization;

5140 - results in persistent or significant disability or incapacity;

5141 - is a congenital anomaly or birth defect (not applicable in this trial);

5142 - other important events that may jeopardize the safety of the subject or may require

5143 intervention to prevent one of the outcomes listed above.

5144

5145 All SAEs will be reported, as described below (9.2.1), by the principle investigator to the Data

5146 Monitoring Committee (DMC) and to the accredited METC that approved the protocol,

5147 according to the requirements of that METC.

5148

5149 9.2.1 Context-specific SAE reporting

5150 This study population (critically ill preterm infants) has a high risk of serious complications

5151 (so-called "context-specific SAE's"), which are inherent to their vulnerable condition and

5152 unrelated to the intervention which is under evaluation in this trial.

5153 These complications are included in the primary and secondary outcomes of this study and

5154 are recorded in the Case Report Form. This documentation will include the date of diagnosis,

5155 classification/gradation of the complication, type of action taken if appropriate (with some

5156 complications a wait and see approach is warranted). Since these complications are highly
5157 interrelated and of longitudinal character, it is impossible to indicate an exact date for the
5158 resolution or stabilisation of each specific diagnosis. Therefore, we will use the date of
5159 discharge from the NICU for this purpose. As long as the child is admitted to the NICU, the
5160 complication will be classified as ongoing.

5161 In light of the above, immediate and individual reporting of all these condition related
5162 complications will not enhance the safety of study.^{1,2} This is also in accordance with CCMO
5163 regulations (<http://www.ccmo-online.nl/main.asp?pid=25&sid=49&ssid=178>)

5164 The context-specific SAEs that will be identified include the events listed under paragraph
5165 7.7.2, on page 27 and 28 of the protocol.

5166 Once a year, an overview of the aforementioned complications for each treatment arm and
5167 ordered by organ system will be presented to the DMC and METC. This overview will consist
5168 of the following information: name of the complication, date of diagnosis,
5169 classification/gradation of the complication, type of action taken, date of discharge or
5170 ongoing.^{53,54}

5171 9.2.2 Suspected unexpected serious adverse reactions (SUSAR)

5172 Adverse reactions are all untoward and unintended responses to an investigational product
5173 related to any dose administered.

5174

5175 Unexpected adverse reactions are adverse reactions, of which the nature, or severity, is not
5176 consistent with the applicable product information (see SPC/IMPD) or the context-specific
5177 SAEs listed in paragraph 9.2.1.

5178

5179 Any SUSAR should be reported, as soon as it occurs, to the principle investigator and the
5180 study coordinator via the study website (**Alert Procedure**, see paragraph 9.4). The PI will
5181 report expedited all SUSARs through the web portal ToetsingOnline to the METC, competent
5182 authority, Medicine Evaluation Board as well as to the competent authorities in other
5183 Member States, according to the requirements of the Member States.

5184 The expedited reporting will occur not later than 15 days after the PI has first knowledge of
5185 the adverse reactions. For fatal or life threatening cases the term will be maximal 7 days for
5186 a preliminary report with another 8 days for completion of the report.

5187

5188 9.2.3 Annual safety report

5189 In addition to the expedited reporting of SUSARs, the PI will submit, once a year throughout
5190 the clinical trial, a safety report to the DMC, accredited METC, competent authority,
5191 Medicine Evaluation Board and competent authorities of the concerned Member States as
5192 well as the investigators of all participating centers.

5193 This safety report consists of:

- 5194 – a list of all suspected (unexpected or expected) serious adverse reactions, along with an
5195 aggregated summary table of all reported serious adverse reactions
- 5196 – a report concerning the safety of the subjects, consisting of a complete safety analysis
5197 and an evaluation of the balance between the efficacy and the harmfulness of the
5198 medicine under investigation.

5199

5200 **9.3 Follow-up of adverse events**

5201 All adverse events will be followed until they have abated, or until a stable situation has
5202 been reached. Depending on the event, follow up may require additional tests or medical
5203 procedures as indicated. According to the standard of care, all infants will participate in the
5204 usual NICU follow-up program. This program is targeted at evaluating and coordinating
5205 diagnostic procedures and treatment of all prematurity related problems, in close
5206 cooperation with regional and local pediatricians.

5207

5208 **9.4 Data Monitoring Committee (DMC), the Alert Procedure**

5209 An external Data Monitoring Committee (DMC) will monitor efficacy and safety outcomes
5210 and will provide the trial's Steering Committee with recommendations regarding continuing
5211 or stopping the trial (for all patients or subgroups of patients) when approximately 25%
5212 (safety only), 50% (safety and efficacy) and 75% (safety and efficacy) of the anticipated
5213 outcome data are available. Data summaries for the DMC will be prepared by a statistician
5214 who is not a member of the investigating team. The safety data will include, but not be
5215 restricted to, serious adverse events and the safety outcomes listed as secondary outcomes.
5216 The DMC will be blinded to the treatment allocation. During the closed DMC meetings, the
5217 data manager will be stand-by to reveal the allocation labels if the DMC thinks this is
5218 necessary. If the DMC recommends modification or cessation of the study protocol, this will
5219 be discussed with the Steering Committee, who will make the decision. The DMC will be
5220 composed of 3 individuals: a neonatologist with extensive knowledge of BPD, a statistician
5221 who has experience with trials, and some experience on previous DMCs and a
5222 pharmacologist with extensive knowledge of the use of hydrocortisone (corticosteroids) in
5223 neonates. The Steering Committee will propose a detailed mandate and review this with the
5224 DMC, from the outset. Identification and circulation of external evidence (e.g., from other

5225 trials/systematic reviews) is not the responsibility of the DMC members. It is the

5226 responsibility of the PI to provide any such information to the DMC.

5227

5228 To enhance the safety of patients in the STOP-BPD trial, a special alert procedure has been

5229 added to the CRF and the website (SUSAR), "The Alert Procedure". This tool is used to

5230 monitor special conditions and acute situations that need the direct attention of the

5231 principle investigator and the study coordinator. If necessary the Steering Committee can

5232 decide to alert the DMC. Furthermore, the Steering Committee will provide a summary

5233 report after every 10 alerts to the DMC.

5234

5235 There are 5 situations when the **Alert Procedure** must be used:

5236 11. Any synchronous use of indomethacin/ibuprofen and study medication

5237 12. Any intestinal perforation occurring during or after the study medication treatment

5238 course

5239 13. Occurrence of hypertension as defined

5240 14. Any use of open label hydrocortisone

5241 15. Occurrence of a SUSAR

5242

5243 The "Alert Procedure" will run in the background for the first 4 conditions. CRF data will be

5244 linked automatically and an email will be send to principal investigator and the study

5245 coordinator automatically once conditions 1 to 4 occur. In case of a SUSAR the local

5246 investigator can alert the principal investigator and the study coordinator via a SUSAR email

5247 button on the trial website.

5248

5249 **10. ETHICAL CONSIDERATIONS**

5250 **10.1 Regulation statement**

5251 The study will be conducted according to the principles of the Declaration of Helsinki⁵⁵ and
5252 in accordance with the Medical Research Involving Human Subjects Act (WMO).

5253

5254 **10.2 Recruitment and informed consent**

5255 Patients will be recruited and their parents will be informed and asked for consent by the
5256 attending paediatricians. Informed written consent must be obtained from the parents prior to
5257 randomisation for the study. The patient information letter and informed consent are provided
5258 in section I of the study dossier. The right of a parent or patient to refuse participation without
5259 giving reasons will be respected. The parents will remain free to withdraw their child at any
5260 time from the study without consequences for further treatment.

5261

5262 **10.3 Benefits and risks assessment, group relatedness**

5263 Burden: All infants participating in (either treatment arm of) the study are subjected to
5264 routine neonatal intensive care. The administration of the study intervention itself
5265 (hydrocortisone or placebo administration) does not pose an extra burden on the patients
5266 since intravenous access will be necessary for other clinical reasons. If this is no longer the
5267 case, study medication may be administered via the oral route. This study does not require
5268 extra investigations or interventions.

5269 Benefit and risks: Hydrocortisone may facilitate extubation and thereby reduce the total
5270 duration of mechanical ventilation. In addition, hydrocortisone may reduce the incidence of
5271 BPD. Both these beneficial effects may improve neurodevelopmental outcome. On the other
5272 hand, use of hydrocortisone may increase the risk for (often transient) hyperglycemia,
5273 hypertension and systemic infection. Although the increased risk of gastrointestinal

5274 perforation has up to now only been reported during the early (within the first 96 hours of
5275 life) administration of corticosteroids, the risk may also be increased when administering
5276 hydrocortisone after the first week of life. Finally, early (within the first 96 hours of life) use
5277 of dexamethasone has been associated with an increase risk for neurodevelopmental
5278 sequelae. Historical cohort studies investigating the use of hydrocortisone after the first
5279 week of life have found no evidence to support this. Infants assigned to the placebo group
5280 will not benefit from the aforementioned possible beneficial effects nor be subjected to the
5281 possible adverse effect of hydrocortisone.

5282 Group relatedness: BPD is a complication occurring exclusively in preterm infants. Any
5283 intervention aiming to reduce the risk of this complication therefore needs to be studied in
5284 this specific population at risk.

5285

5286 **10.4 Compensation for injury**

5287 The sponsor/investigator has a liability insurance which is in accordance with article 7,
5288 subsection 6 of the WMO. The sponsor (also) has an insurance which is in accordance with
5289 the legal requirements in the Netherlands (Article 7 WMO and the Measure regarding
5290 Compulsory Insurance for Clinical Research in Humans of 23rd June 2003). This insurance
5291 provides cover for damage to research subjects through injury or death caused by the study.

- 5292 1. € 450.000,-- (i.e. four hundred and fifty thousand Euro) for death or injury for each
5293 subject who participates in the Research;
- 5294 2. € 3.500.000,-- (i.e. three million five hundred thousand Euro) for death or injury for all
5295 subjects who participate in the Research;
- 5296 3. € 5.000.000,-- (i.e. five million Euro) for the total damage incurred by the organization
5297 for all damage disclosed by scientific research for the Sponsor as ‘verrichter’ in the
5298 meaning of said Act in each year of insurance coverage.

5299 The insurance applies to the damage that becomes apparent during the study or within 4 years
5300 after the end of the study.

5301

5302 **10.5 Incentives**

5303 Participants will not receive a financial compensation for participation as an incentive.

5304

5305 **11. ADMINISTRATIVE ASPECTS AND PUBLICATION**

5306 **11.1 Handling and storage of data and documents**

5307 Datamanagement will be implemented according to Good Clinical Practice (GCP)-guidelines.

5308 Patient data will be entered by way of an eCRF in a central GCP proof internet based

5309 database to facilitate on-site data-entry. Security is guaranteed with login names, login

5310 codes and encrypted data transfer. An experienced datamanager will maintain the database

5311 and check the information in the database for completeness, consistency and plausibility.

5312

5313 The data of all subjects will be coded and this coding will not be retraceable to the individual

5314 patient. The key to this coding is safeguarded by the investigator. A limited number of

5315 people have access to the source data. These are the principal investigator, investigating

5316 doctor and investigating personnel. Personal data are only processed by the researchers or

5317 by those who fall directly under their authority. In addition, the study monitor, quality

5318 assurance auditor, employees from the METC and the Health Care Inspectorate of the

5319 Ministry of Health, welfare and Sport (Nederlandse Inspectie voor de Gezondheidszorg) have

5320 access to the source data. All are subject to the pledge of confidentiality. Data and human

5321 material will be stored for 15 years strictly confidential.

5322

5323 **11.2 Amendments**

5324 Amendments are changes made to the trial after a favourable opinion by the accredited METC

5325 has been given. All amendments will be notified to the METC that gave a favourable opinion.

5326 All substantial amendments will be notified to the METC and to the competent authority.

5327 Non-substantial amendments will not be notified to the accredited METC and the competent

5328 authority, but will be recorded and filed by the Steering Committee.

5329

5330 **11.3 Annual progress report**

5331 If requested, an annual progress report of the progress of the trial will be provided to the

5332 accredited METC. Information will be provided on the date of inclusion of the first subject,

5333 numbers of subjects included and numbers of subjects that have completed the trial, serious

5334 adverse events/ serious adverse reactions, other problems, and amendments. In case the study

5335 is ended prematurely, the investigator will notify the accredited METC, including the reasons

5336 for the premature termination. Within one year after the end of the study, the

5337 investigator/sponsor will submit a final study report with the results of the study, including

5338 any publications/abstracts of the study, to the accredited METC.

5339

5340 **11.4 Public disclosure and publication policy**

5341 The study will be registered in the EUDRACT, the website of the Dutch National Competent

5342 Authority, the 'Centrale Commissie Mensgebonden Onderzoek' (CCMO), Dutch public trial

5343 registry, part of the WHO registry. The results of the study will be published in peer-

5344 reviewed international medical journals. In addition, the results of the study will be used for

5345 development and implementation of a guideline on treatment of BPD, which will benefit

5346 future patients.

5347

5348 **12. ORGANISATION**

5349 **12.1 Steering Committee**

5350 The Steering Committee is the main policy and decision making committee of the study and
5351 has final responsibility for the scientific conduct of the study. It will be composed of
5352 representatives of the sponsor, of the investigators of the participating centres and of the
5353 MCRN. The specific tasks of the Steering Committee are:

- 5354 • Approve the study protocol
- 5355 • Approve necessary changes in the protocol based on considerations of feasibility
- 5356 • Act upon recommendations of the Data Monitoring Committee
- 5357 • Review performance reports of the study sites
- 5358 • Resolve operational problems brought before it by the project manager
- 5359 • Approve study reports and papers for publication.

5360

5361 **12.2 Data Monitoring Committee**

5362 An independent Data Monitoring Committee (DMC) will be created specifically for this trial.
5363 The DMC will act in advisory capacity to the Steering Committee. See Paragraph 9.4 for a
5364 description of the membership, tasks and responsibilities of the DMC.

5365

5366 **12.3 Clinical Project Manager / Central Study Coordinator**

5367 An experienced clinical project manager (CPM) from MCRN will manage the quality of the
5368 study according to the Good Clinical Practice (GCP)-guidelines, supervise the data monitoring
5369 process, and verify the quality of conduct of all study personnel. The CPM and/or clinical
5370 research associate (CRA) will arrange that the study personnel is adequately trained in GCP

5371 and study protocol, where needed. The CPM meets regularly with the CRA, data managers,
5372 the Data Safety Monitoring Committee (DSMC), financial departments of study centers, and
5373 all other relevant parties to assure study progress, quality and financials are according to
5374 planning. The CPM will coordinate regulatory authority and ethics committee submissions.
5375 The CPM provides regularly an overall study status report to the Steering Committee

5376

5377 **12.4 Study Monitoring**

5378 The study will be monitored by an experienced monitor from MCRN throughout its duration
5379 by means of personal visits to the Investigator's facilities and through other communications
5380 (e.g., telephone calls, written correspondence).

5381 Monitoring visits will be scheduled at mutually agreeable times periodically throughout the
5382 study and at frequency deemed appropriate for the study.

5383 These visits will be conducted to evaluate the progress of the study, ensure the rights and
5384 wellbeing of the subjects are protected, check that the reported clinical study data are
5385 accurate, complete and verifiable from source documents, and the conduct of the study is in
5386 compliance with the approved protocol and amendments, GCP and applicable national
5387 regulatory requirements. A monitoring visit will include a review of the essential clinical
5388 study documents (regulatory documents, CRFs, source documents, drug disposition records,
5389 subject informed consent forms, etc.) as well as discussion on the conduct of the study with
5390 the Investigator and staff. The Investigator and staff should be available during these visits to
5391 facilitate the review of the clinical study records and resolve/document any discrepancies
5392 found during the visit.

5393

5394 **12.5 Quality Assurance Audits and Inspections**

5395 The Sponsor's (or an authorized representative's) Quality Assurance department may conduct
5396 audits of all aspects of the clinical study either during the study or after the study has been
5397 completed. By participating this trial the investigator agrees to this requirement.
5398 The clinical study may also be subject to inspection by regulatory authorities as well as the
5399 accredited Medical Ethical Committee/ Competent authority to ascertain that the study is
5400 being or has been conducted in accordance with protocol requirements, GCP, as well as the
5401 applicable regulatory requirements.
5402
5403

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APPENDIX 1 STUDIE MEDICATIE SCHEMA

| Step 1: Fill in patient data in yellow cubicles. Use weight at day of randomization. | | Step 2: Fill in date and time of first administration study medication in green cubicle. Format for filling date/time: dd-mm-yyyy hr:mm | | Step 3: In case of hypertension related to study medication, fill in the red cubicle. The program will automatically skip the next dose and commence the following dose with a lower daily frequency. | | Step 4: For print out of study medication list, press: <input type="button" value="Print"/> | | | |
|--|--|---|----------|---|----------------|---|---------------|----------|---------------|
| Study identification | | First administration | | | |  | | | |
| Name | | Date/time | | | | | | | |
| Date of birth | | Lowering dosage regimen | | | | | | | |
| Weight | | Date/time | | | | | | | |
| gram | | | | | | | | | |
| Day in regimen | Time | Times per day | mg/dose | Daily dose/kg | Day in regimen | Time | Times per day | mg/dose | Daily dose/kg |
| Day 1 | 0-01-00 0:00 0-01-00 6:00 0-01-00 12:00 0-01-00 18:00 | 4 x | 0.00 mg. | 5 mg/kg/d | Day 8 | 7-01-00 0:00 7-01-00 8:00 7-01-00 16:00 | 3 x | 0.00 mg. | 3.75 mg/kg/d |
| Day 2 | 1-01-00 0:00 1-01-00 6:00 1-01-00 12:00 1-01-00 18:00 | 4 x | 0.00 mg. | 5 mg/kg/d | Day 9 | 8-01-00 0:00 8-01-00 8:00 8-01-00 16:00 | 3 x | 0.00 mg. | 3.75 mg/kg/d |
| Day 3 | 2-01-00 0:00 2-01-00 6:00 2-01-00 12:00 2-01-00 18:00 | 4 x | 0.00 mg. | 5 mg/kg/d | Day 10 | 9-01-00 0:00 9-01-00 8:00 9-01-00 16:00 | 3 x | 0.00 mg. | 3.75 mg/kg/d |
| Day 4 | 3-01-00 0:00 3-01-00 6:00 3-01-00 12:00 3-01-00 18:00 | 4 x | 0.00 mg. | 5 mg/kg/d | Day 11 | 10-01-00 0:00 10-01-00 8:00 10-01-00 16:00 | 3 x | 0.00 mg. | 3.75 mg/kg/d |
| Day 5 | 4-01-00 0:00 4-01-00 6:00 4-01-00 12:00 4-01-00 18:00 | 4 x | 0.00 mg. | 5 mg/kg/d | Day 12 | 11-01-00 0:00 11-01-00 8:00 11-01-00 16:00 | 3 x | 0.00 mg. | 3.75 mg/kg/d |
| Day 6 | 5-01-00 0:00 5-01-00 6:00 5-01-00 12:00 5-01-00 18:00 | 4 x | 0.00 mg. | 5 mg/kg/d | Day 13 | 12-01-00 0:00 12-01-00 12:00 | 2 x | 0.00 mg. | 2.5 mg/kg/d |
| Day 7 | 6-01-00 0:00 6-01-00 6:00 6-01-00 12:00 6-01-00 18:00 | 4 x | 0.00 mg. | 5 mg/kg/d | Day 14 | 13-01-00 0:00 13-01-00 12:00 | 2 x | 0.00 mg. | 2.5 mg/kg/d |
| | | | | | Day 15 | 14-01-00 0:00 14-01-00 12:00 | 2 x | 0.00 mg. | 2.5 mg/kg/d |
| | | | | | Day 16 | 15-01-00 0:00 15-01-00 12:00 | 2 x | 0.00 mg. | 2.5 mg/kg/d |
| | | | | | Day 17 | 16-01-00 0:00 16-01-00 12:00 | 2 x | 0.00 mg. | 2.5 mg/kg/d |
| | | | | | Day 18 | 17-01-00 0:00 | 1 x | 0.00 mg. | 1.25 mg/kg/d |
| | | | | | Day 19 | 18-01-00 0:00 | 1 x | 0.00 mg. | 1.25 mg/kg/d |
| | | | | | Day 20 | 19-01-00 0:00 | 1 x | 0.00 mg. | 1.25 mg/kg/d |
| | | | | | Day 21 | 20-01-00 0:00 | 1 x | 0.00 mg. | 1.25 mg/kg/d |
| | | | | | Day 22 | 21-01-00 0:00 | 1 x | 0.00 mg. | 1.25 mg/kg/d |

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5564 **APPENDIX 2**

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5566 **Oxygen reduction test**

5567 Bronchopulmonary dysplasia (BPD) can be classified in to mild, moderate or severe
5568 depending on the amount and duration of supplemental oxygen and the level of respiratory
5569 support. If a patient has received supplemental oxygen for more than 28 d ($FiO_2 > 0.21$ for
5570 more than 12 hours each day) and is receiving no extra oxygen at 36 weeks postmenstrual
5571 age (PMA), he or she is classified as having mild BPD. If the oxygen need at 36 weeks PMA is
5572 between 0.21 and 0.30, BPD is classified as moderate and in case of a $FiO_2 > 0.30$ and/or
5573 receiving continuous positive airway pressure (nCPAP)/mechanical ventilation as severe.
5574 It is important to realize that the duration of supplemental oxygen is highly dependent on
5575 target ranges of transcutaneous oxygen saturation (SpO_2) and the alertness of the clinician
5576 to actively wean oxygen delivery.
5577 To make sure that patients receive supplemental oxygen for pulmonary reasons and to
5578 standardize the amount of oxygen to predefined and uniform SpO_2 targets, Walsh et al.
5579 developed a so-called oxygen reduction test at 36 weeks PMA. Patients are eligible for
5580 testing if they need a FiO_2 between 0.21 and 0.30 to maintain the SpO_2 between 90-96% **or** if
5581 they receive a $FiO_2 > 0.30$ resulting in a $SpO_2 > 96\%$. Patients supported with nasal cannulae
5582 (flow not nCPAP) without supplemental oxygen, and patients treated with
5583 nCPAP/mechanical ventilation or with a $FiO_2 > 0.30$ resulting in a $SpO_2 < 96\%$ do not need
5584 additional testing, and are, respectively, classified as having mild and severe BPD.

5585 ***The oxygen reduction test***5586 **Indications:**

5587 - $\text{FiO}_2 > 0.21$ and < 0.30 with oxygen saturation ranges between 90% and 96%

5588 - $\text{FiO}_2 > 0.30$ with a oxygen saturation range above 96%

5589 Methods:

5590 The patient is placed in supine position and the test is initiated 30 minutes after a feeding. The

5591 supplemental oxygen requirement will be gradually weaned to room air while monitoring

5592 SpO_2 . The diagnosis moderate BPD can be rejected when the SpO_2 remain above $\geq 88\%$ in

5593 room air during 1 hour without apnea or bradycardia.

5594 The diagnosis moderate BPD is confirmed if the saturation goes below 80% during > 1 minute

5595 or remains between 80-87% during > 5 minutes. All occurrences of movement artifact

5596 (defined as visible motion of the infant together with loss of plethysmograph signal from the

5597 monitor) are recorded and corresponding saturation values are to be deleted.

5598

5599 The test contains 4 phases

5600 Phase 1: Baseline evaluation

5601 For 15 minutes heart rate, respiratory rate, SpO_2 , number of apnea (cessation of breathing $>$

5602 20 seconds) and bradycardia (heart rate $< 80/\text{min}$ during > 10 sec) will be collected.

5603 Phase 2: Oxygen reduction

5604 The supplemental oxygen will be weaned by 2% to room air, after which the flow will be

5605 weaned with 0.1 L/min to 0 L/min; The nasal cannulae will be removed from the nares, but

5606 not removed from the face.

5607 Phase 3: Observation period

5608 For the period of 1 hour the heart rate, respiratory rate, and SpO_2 in room air will be

5609 registered. In case of a desaturation below 80% for > 1 minute or saturation between 80-87%

5610 for > 5 minutes, the supplemental oxygen will be restarted and the test will be aborted.

5611 *Phase 4: Back to situation before the test*

5612 The level of supplemental oxygen and flow will be reset to the status before the test.

5613