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# Identifying effect modifiers of systemic hydrocortisone treatment initiated 7–14 days after birth in ventilated very preterm infants on long-term outcome: secondary analysis of a randomised controlled trial

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## ABSTRACT

**Objective** To explore clinical effect modifiers of systemic hydrocortisone in ventilated very preterm infants for survival and neurodevelopmental outcome at 2 years' corrected age (CA).

**Design** Secondary analysis of a randomised placebo-controlled trial.

**Setting** Dutch and Belgian neonatal intensive care units.

**Patients** Infants born <30 weeks' gestational age (GA), ventilator-dependent in the second week of postnatal life.

**Intervention** Infants were randomly assigned to systemic hydrocortisone (cumulative dose 72.5 mg/kg; n=182) or placebo (n=190).

**Main outcome measures** The composite of death or neurodevelopmental impairment (NDI) at 2 years' CA and its components. Candidate effect modifiers (GA, small for GA, respiratory index, sex, multiple births, risk of moderate/severe bronchopulmonary dysplasia or death) were analysed using regression models with interaction terms and subpopulation treatment effect pattern plots.

**Results** The composite outcome was available in 356 (96.0%) of 371 patients (one consent withdrawn). For this outcome, treatment effect heterogeneity was seen across GA subgroups (<27 weeks: hydrocortisone (n=141) vs placebo (n=156), 54.6% vs 66.2%; OR 0.61 (95% CI 0.38 to 0.98); ≥27 weeks: hydrocortisone (n=30) vs placebo (n=31), 66.7% vs 45.2%; OR 2.43 (95% CI 0.86 to 6.85); p=0.02 for interaction). This effect was also found for the component death (<27 weeks: 20.1% vs 32.1%; OR 0.53 (95% CI 0.32 to 0.90); ≥27 weeks: 28.1% vs 16.1%; OR 2.04 (95% CI 0.60 to 6.95); p=0.049 for interaction) but not for the component NDI. No differential treatment effects were observed across other subgroups.

**Conclusion** This secondary analysis suggests that in infants <27 weeks' GA, systemic hydrocortisone may improve the outcome death or NDI, mainly driven by its

## WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ The SToP-BPD (Systemic Hydrocortisone To Prevent Bronchopulmonary Dysplasia in preterm infants) Study showed no difference in the primary composite outcome death or bronchopulmonary dysplasia and long-term composite outcome death or neurodevelopmental impairment (NDI) at 2 years' corrected age between both allocation groups in the total study population of infants born <30 weeks' gestation or with a birth weight <1250 g.
- ⇒ Previous subgroup analysis of the SToP-BPD Study at 36 weeks' postmenstrual age suggested a reduced death rate in favour of hydrocortisone in the gestational age subgroup below 27 weeks.
- ⇒ Identifying factors that modify hydrocortisone treatment effect is important as it will allow selection of subsets of patients with a potential better or worse benefit–harm balance.

## WHAT THIS STUDY ADDS

- ⇒ This secondary analysis of the SToP-BPD trial suggests a potential beneficial systemic hydrocortisone treatment effect in the subgroup of ventilated preterm infants born before 27 weeks' gestation on the long-term composite outcome death or NDI, mainly driven by its component death.

## HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ⇒ The findings of this study provide further guidance for larger future clinical trials on postnatal corticosteroids to prevent bronchopulmonary dysplasia in patients with certain risk factors.

component death. There was insufficient evidence for other selected candidate effect modifiers.

## INTRODUCTION

Bronchopulmonary dysplasia (BPD) remains the most common morbidity of extreme prematurity.<sup>1,2</sup> Its pathogenesis is multifactorial, but pulmonary inflammation is considered an important risk factor.<sup>3</sup> Because of their anti-inflammatory effects, corticosteroids have been studied for the prevention and treatment of BPD.<sup>4,5</sup> The corticosteroid dexamethasone reduces the risk of BPD,<sup>4</sup> but has also been associated with an increased incidence of neurodevelopmental impairment (NDI).<sup>6–8</sup> The SToP-BPD (Systemic Hydrocortisone To Prevent Bronchopulmonary Dysplasia in preterm infants) Study investigated if systemic hydrocortisone, started in the second week after birth in ventilator-dependent very preterm infants, would be an effective and safe alternative. It showed that hydrocortisone did not reduce the risk of death or BPD at 36 weeks' postmenstrual age (PMA),<sup>9</sup> and did not increase the risk of death or NDI at 2 years' corrected age (CA).<sup>10</sup>

The estimated overall treatment effect of the SToP-BPD Study reflects the average effect for the total study population. Yet, it is conceivable that infants with different characteristics may respond differently to the same intervention. Identifying factors that modify hydrocortisone treatment effect is important as it will allow selection of subsets of patients with a potential better or worse benefit–harm balance. Previous subgroup analysis of the SToP-BPD Study at 36 weeks' PMA for preselected patient characteristics suggested a differential treatment effect for the primary outcome component death across gestational age (GA) subgroups.<sup>9</sup> This illustrates that the treatment effect of hydrocortisone may vary across subpopulations of infants. It is unclear if effect modification also applies to the long-term outcome. Therefore, the objective of the current study was to explore potential clinical effect modifiers of hydrocortisone treatment on long-term survival and neurodevelopmental outcome at 2 years' CA of infants included in the SToP-BPD Study.

## METHODS

### Study population

The SToP-BPD Study is a double-blind, placebo-controlled, randomised trial, which was performed between November 2011 and December 2016 in 16 neonatal intensive care units in the Netherlands and Belgium.<sup>9,11</sup> It included infants born with a GA less than 30 weeks and/or with a birth weight below 1250 g who were ventilator dependent in the second week of life. Infants were randomly assigned to receive either a 22-day course of systemic hydrocortisone (cumulative dose 72.5 mg/kg) or placebo.

### Key long-term composite outcome and its individual components

Follow-up assessment at 2 years' CA was performed between April 2014 and June 2019. The key long-term outcome concerned the composite of death or NDI at 2 years' CA and its individual components. The estimated overall treatment effect on these outcomes was published previously.<sup>10</sup> NDI was defined as presence of one or more of the following: cognitive and/or motor composite score less than 85 on the Bayley Scales of Infant and Toddler Development Third Edition, Dutch version; cerebral palsy greater than level II on the Gross Motor Function Classification System; hearing or visual impairment. More

details on definitions can be found in the online supplemental file 2.

### Candidate treatment effect modifiers

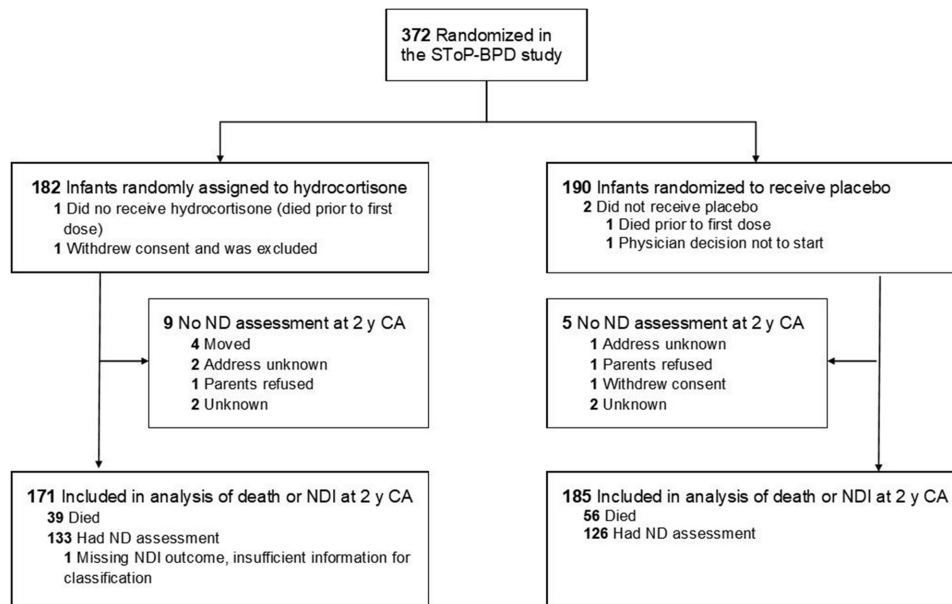
Candidate treatment effect modifiers included the preselected risk factors GA, small for GA (SGA) (<10th percentile Fenton growth chart), respiratory index (mean airway pressure $\times$ fraction of inspired oxygen (FiO<sub>2</sub>)) at randomisation, sex and multiple pregnancies (online supplemental file 2).<sup>12</sup> Information on the preselected risk factors parental education and multilingual environment was missing for the deceased infants; therefore, these were not included. The included candidate treatment effect modifiers are postulated, biologically plausible risk factors for BPD and death.<sup>11,13</sup> BPD is considered an important modifier of long-term outcome and is associated with neurodevelopmental delay.<sup>14</sup>

To evaluate whether the a priori risk of BPD would modulate the effect of hydrocortisone on survival and neurodevelopmental outcome, the Neonatal BPD Outcome Estimator, developed by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Neonatal Research Network was post hoc selected as a candidate effect modifier.<sup>15</sup> This composite risk score considers the simultaneous impact of GA, birth weight, race/ethnicity, sex, respiratory support and FiO<sub>2</sub> on the outcome death or BPD. Combination of individual risk factors in a composite risk score predicts more accurately the underlying individual infants' BPD risk and facilitates analysis across different risk distributions.<sup>16</sup> Since we had only access to the equation for postnatal day 1 and day 3, we used the model at postnatal day 3 and the respiratory settings at randomisation to calculate the individual predicted probability of moderate/severe BPD or death of each individual infant.

### Statistical analysis

Data analyses were performed in the intention-to-treat population, including all randomised patients regardless of protocol deviations or use of open-label corticosteroids. Subgroups were categorised using prespecified cut-off points: GA groups (<27,  $\geq$ 27 weeks), SGA (yes, no), respiratory index ( $\leq$ median, >median of the total study population), sex (male, female) and multiple pregnancies (multiple births, singleton).<sup>12</sup> Crude relative and absolute treatment effect estimates within subgroups were calculated with the corresponding 95% CI. Treatment effect heterogeneity across subgroups was statistically tested through the corresponding (treatment $\times$ subgroup) interaction effect in a logistic regression model and generalised linear model including treatment, subgroup and (treatment $\times$ subgroup) interaction term (online supplemental file 3).<sup>12</sup> Within-subgroup treatment effects are estimated independent of whether the test of the specific interaction term is statistically significant.

Since dichotomising continuous variables may obscure important information that is contained across the full continuum of values, we explored post hoc treatment effect heterogeneity according to the candidate effect modifiers across their full spectrum of values, using subpopulation treatment effect pattern plots (STEPP).<sup>17</sup> STEPP is a non-parametric, graphical approach which constructs overlapping patient subpopulations along the continuum of the covariate, that is, a 'sliding-window' pattern of subpopulations. STEPP analysis improves the precision of the estimated treatment effects within the subgroups by plotting treatment effect estimates against the median values of the specific covariate in the subpopulations to provide a graphical presentation of the heterogeneity of treatment effects. STEPP



**Figure 1** Consolidated Standards of Reporting Trials flow diagram. CA, corrected age; ND=neurodevelopmental; NDI, neurodevelopmental impairment; SToP-BPD, Systemic Hydrocortisone To Prevent Bronchopulmonary Dysplasia in preterm infants.

makes no prior assumptions regarding the pattern of interaction and thus has the potential to highlight complex associations.<sup>18</sup> The STEPP analyses were performed according to the general guidelines as described by Yip *et al.*<sup>17</sup> Subpopulations were chosen using two window smoothing parameters  $r_2$  and  $r_1$ , that is, a sample size of 100 infants per subset ( $r_2$ ) and an overlap of 50 infants ( $r_1$ ) between subsequent subsets, to create a minimum of four to five subgroups with 50% overlap. For a formal interaction test, the  $p$  value for interaction from a supremum test statistic is reported. To assess the consistency of the results, sensitivity analyses with varying sample size ( $r_2$ ) and varying overlap ( $r_1$ ) were performed.

All analyses were performed using two-sided tests and  $p < 0.05$  was regarded as statistically significant; as the analyses were hypothesis generating only, we did not adjust for multiple testing. Statistical analysis was performed in SPSS Statistics for Windows, V.28.0 (IBM Corp), R V.4.1.3 for Windows (R-package stepp and lattice; R Foundation for Statistical Computing) and RStudio.

## RESULTS

The composite outcome death or NDI at 2 years' CA was available in 356 (96.0%) of 371 infants; 95 infants died before 2 years' follow-up, and neurodevelopment assessment was performed in 262 infants (one infant had a missing NDI outcome) (figure 1). Baseline characteristics of both treatment groups were similar, except for more multiple births in the hydrocortisone group (table 1).

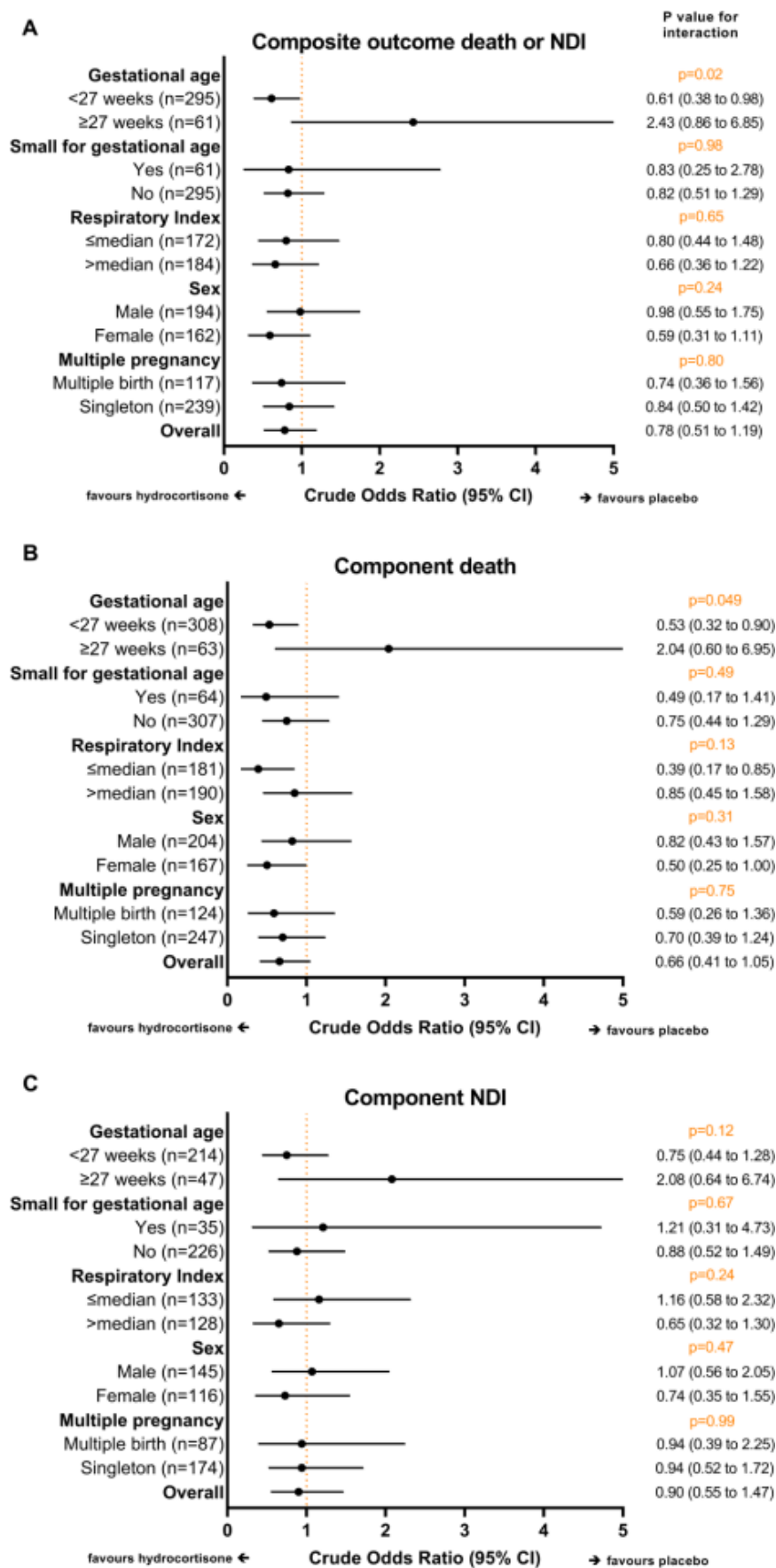
Subgroup analyses showed a differential treatment effect across the dichotomised GA subgroups for the composite outcome of death or NDI at 2 years' CA, with a reduced rate in infants born before 27 weeks' gestation in the hydrocortisone group compared with the placebo group (<27 weeks: hydrocortisone ( $n=141$ ) vs placebo ( $n=156$ ), 54.6% vs 66.2%, crude absolute risk difference (ARD)  $-11.6\%$  (95% CI  $-22.4\%$  to  $-0.5\%$ ), crude OR 0.61 (95% CI 0.38 to 0.98); and  $\geq 27$  weeks: hydrocortisone ( $n=30$ ) vs placebo ( $n=31$ ), 66.7% vs 45.2%, crude ARD 21.5% (95% CI  $-3.2\%$  to 42.8%), crude OR 2.43 (95% CI 0.86 to 6.85);  $p=0.02$  for interaction tests) (figure 2A and online supplemental tables S1 and S2). This was

also found for the component death (hydrocortisone vs placebo: <27 weeks, 20.1% vs 32.1%, crude ARD  $-11.9\%$  (95% CI  $-21.4\%$  to  $-2.1\%$ );  $\geq 27$  weeks, 28.1% vs 16.1%; crude ARD 12.0% (95% CI  $-8.8\%$  to 31.5%),  $p=0.04$  for interaction test; crude OR <27 weeks, 0.53 (95% CI 0.32 to 0.90); crude OR  $\geq 27$  weeks, 2.04 (95% CI 0.60 to 6.95),  $p=0.049$  for interaction test), but not for the NDI component (figure 2B,C and online supplemental tables S1 and S2). No differential treatment effects were observed across the subgroups of other preselected categorical candidate effect modifiers (figure 2A–C and online supplemental tables S1 and S2).

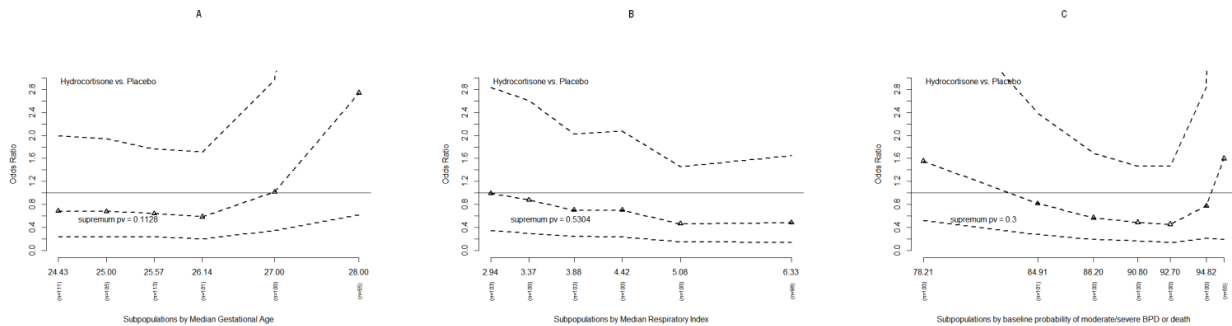
In line with the dichotomised GA subgroup analysis, STEPP suggested treatment effect heterogeneity for the composite outcome death or NDI and its component death, with benefit of

**Table 1** Clinical characteristics at birth and at randomisation of infants with a composite outcome death or neurodevelopmental impairment at 2 years' corrected age

	Hydrocortisone (n=171)	Placebo (n=185)
Infant characteristics		
Gestational age, median (IQR), weeks	25.4 (24.9–26.4)	25.6 (24.7–26.4)
Birth weight, median (IQR), g	777 (640–865)	710 (628–810)
Male sex, n (%)	89 (52.0)	105 (56.8)
Small for gestational age, n (%)*	24 (14.0)	37 (20.0)
Multiple births, n (%)	66 (38.6)	51 (27.6)
Respiratory settings at randomisation		
High-frequency oscillatory ventilation, n (%)	95 (55.6)	86 (46.5)
Fraction of inspired oxygen, median (IQR)	0.35 (0.30–0.45)	0.34 (0.29–0.40)
Respiratory index, median (IQR)†	4.3 (3.3–5.4)	3.9 (3.1–5.0)
Predicted probability of moderate/severe BPD or death, median (IQR), %‡	88.7 (83.1–93.0)	90.2 (85.1–93.4)
*Small for gestational age was defined as birth weight less than the 10th percentile on the Fenton growth chart.		
†Respiratory index was defined as mean airway pressure×fraction of inspired oxygen.		
‡Predicted probability of moderate/severe BPD was calculated using the NICHD Neonatal BPD Outcome Estimator.		
BPD, bronchopulmonary dysplasia; NICHD, Eunice Kennedy Shriver National Institute of Child Health and Human Development.		



**Figure 2** Forest plot of the subgroup analyses of the composite outcome death or neurodevelopmental impairment (NDI) at 2 years' corrected age (A) and its individual components (B,C) at 2 years' corrected age.<sup>a</sup> Subgroup analyses were performed and statistically tested with interaction effect of the specific subgroup and treatment in logistic regression models. P value for interaction is reported.



**Figure 3** STEPP of the heterogeneity of hydrocortisone versus placebo treatment effect by gestational age (A), respiratory index (B) and predicted probability of moderate/severe BPD or death (C) on the long-term outcome death or neurodevelopmental impairment at 2 years' corrected age, based on crude OR estimates.<sup>a</sup> Subpopulations were chosen with sample size  $r2$  of 100 infants per subset and overlap  $r1$  of 50 infants between subsequent subsets. Shown are pointwise estimates and 95% CIs of the OR per subpopulation, plotted at the median value of the corresponding subpopulation. Interaction p values derived from permutation tests with 2500 resampling steps. An OR <1 indicates that hydrocortisone is the preferred strategy. BPD, bronchopulmonary dysplasia; STEPP, subpopulation treatment effect pattern plots.

hydrocortisone treatment across the GA range below 27 weeks, although this did not yield statistical significance (figure 3A and online supplemental figures 1A and 2A). Exploration of patterns of treatment effects for varying levels of respiratory index and probability of moderate/severe BPD or death following the NICHD Neonatal BPD Outcome Estimator suggested no clear treatment heterogeneity across subpopulations for the composite outcome and its individual components (figure 3B,C and online supplemental figures 2 and 3). Sensitivity STEPP analyses yielded results (online supplemental table 3).

## DISCUSSION

This prespecified secondary analysis of the SToP-BPD trial is to our knowledge the first study exploring potential clinical effect modifiers of hydrocortisone treatment initiated in the second week after birth in ventilated very preterm infants for long-term survival and neurodevelopmental outcome. We observed a modifying treatment effect of GA; infants born before 27 weeks' gestation had a significantly reduced rate of the composite outcome death or NDI at 2 years' CA in favour of hydrocortisone, mainly driven by a reduction in death. No other selected candidate treatment effect modifiers showed sufficient evidence of a differential hydrocortisone treatment effect.

Lower GA is an important risk factor for neonatal morbidities, including an inverse relation with impaired neurodevelopmental outcome.<sup>19 20</sup> Consequently, it is conceivable that the most immature infants may have a different risk profile than more mature infants and may respond differently to hydrocortisone treatment. An exploratory analysis of the PREMIOLOC Study, a randomised trial involving prophylactic hydrocortisone treatment, suggested a differential hydrocortisone effect in GA subgroups for neurodevelopmental outcome. The authors reported a significant improvement in neurodevelopmental outcomes following hydrocortisone treatment in the subgroup of infants born at 24–25 weeks' gestation, which was not the case in the subgroup of infants born at 26–27 weeks' gestation.<sup>21</sup> This improvement in neurodevelopment in the specific subgroup of infants born at 24–25 weeks of gestation was not observed in our STEPP for GA. Important differences between the two studies in patient characteristics, dosage and timing of hydrocortisone treatment may explain this discrepancy.

In the initial SToP-BPD Study, subgroup analyses were performed for the primary outcome death or BPD at 36 weeks' PMA and its components.<sup>9</sup> Across categorical GA subgroups (<27 or ≥27 weeks), a differential treatment effect was found

for the component death, with a reduced rate in favour of hydrocortisone in the GA subgroup below 27 weeks. Consistent with this earlier finding at 36 weeks' PMA, the current study also observed a statistically significant and clinically relevant reduction in mortality at 2 years' CA in favour of hydrocortisone in infants born below 27 weeks' gestation. Importantly, our results suggest that this improved survival was not associated with an increased risk of NDI. The small size of the GA subgroup ≥27 weeks and the consequently wide CI provide too little information for inference about the treatment effect in this subgroup.

For further inspection, we used post hoc STEPP analysis to explore the effect of hydrocortisone along the continuum of GA, respiratory index and the probability of moderate/severe BPD or death. STEPP has the advantage over the more conventional approach of categorisation of a continuous covariate, that it provides more insight into the effect along the range of covariate values, and where treatment may be particularly beneficial (or detrimental). STEPP is an exploratory tool, not intended to set specific cut-off points for subgroups, but rather to provide some indication on ranges of values where the treatment effect might have a particular behaviour.<sup>17 18</sup> Hence, it facilitates hypothesis generation and provides guidance for future research. The STEPP of treatment effect heterogeneity for GA supported the results of the prespecified dichotomised subgroup analysis, though not statistically significant. Additional analyses of treatment effect heterogeneity for GA should be considered in other studies of hydrocortisone treatment.

In daily practice, the decision to start postnatal corticosteroids is often guided by the severity of the patients' respiratory condition and the presumed risk of BPD. This is probably based on a meta-regression analysis of randomised controlled trials investigating dexamethasone that suggests that the effect of postnatal corticosteroids on the combined outcome death or cerebral palsy varies with the underlying baseline risk of BPD. Infants at higher risk of BPD seem to benefit from postnatal dexamethasone treatment, while treating infants at low risk of BPD might be harmful.<sup>16</sup> We found no clear treatment effect heterogeneity for the key long-term composite outcome and its components across the range of probabilities for moderate/severe BPD or death, calculated with the NICHD Neonatal BPD Outcome Estimator.<sup>15</sup> This lack of treatment effect heterogeneity may partly be explained by the fact that the SToP-BPD Study included ventilator-dependent very preterm infants with a respiratory index above 2.5. These criteria resulted in a narrow distribution of the probabilities of moderate/severe BPD or death as almost

all infants in our study were classified as high risk. Furthermore, the NICHD Neonatal BPD Outcome Estimator is based on the US population and is not yet validated in the Dutch/Belgian population, so it remains unclear how it will perform in the SToP-BPD Study population. Additional analyses for heterogeneity of the hydrocortisone treatment effect are needed in other clinical studies to gain more insight.

Our study has some limitations. First, the SToP-BPD Study was only powered for the overall treatment effect on the primary composite outcome death or BPD at 36 weeks' PMA.<sup>9</sup> Due to the small numbers within various subgroups, there is limited statistical power to identify subgroups that might have a differential effect of hydrocortisone treatment. Also, except for the randomisation stratification factor GA, interpretation of the other subgroups is hampered by potential confounder imbalance. Therefore, this secondary analysis of the SToP-BPD Study should be regarded as exploratory and hypothesis generating only. Second, STEPP analysis is sensitive to the choices of subgroup sample size ( $r_2$ ) and overlap between subsequent subgroups ( $r_1$ ).<sup>17, 18</sup> However, our sensitivity analyses with varying  $r_1$  and  $r_2$  showed similar patterns of heterogeneity. Third, a relatively high proportion of infants in the placebo group (56.8%) was treated with open-label hydrocortisone, particularly those with a GA below 27 weeks. Although no firm conclusions can be drawn, it is unlikely that this impacted the subgroup analyses, as a previous published meta-regression analysis showed no modulating effect of open-label steroids on long-term outcomes.<sup>22</sup>

## CONCLUSIONS

This secondary analysis of the SToP-BPD trial suggests that in the subgroup of ventilated preterm infants born before 27 weeks' gestation, systemic hydrocortisone initiated in the second week after birth may improve the composite outcome death or NDI, mainly driven by its component death. There was insufficient evidence for the other selected candidate treatment effect modifiers. The findings of this study require confirmation in larger future trials.

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**Contributors** MS, RMS, CK-E, MvS, SM-dT, RNgBT, TM, EB, KS, BWK, AD, MMWV, YM, HG, KP, MO and AGvW-L are local investigators at the participating centres, and made substantial contributions to the concept and design of the study, and interpretation of data. NMH performed the statistical analyses, prepared the data tables, drafted the initial manuscript and revised the manuscript. MPM participated in the statistical analyses, and critically reviewed and revised the manuscript for important intellectual content. WO and AHvK are local investigators who made substantial contributions to the concept and design of the study, had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis, and critically reviewed the manuscript for important intellectual content. All authors approved the final manuscript as submitted. AHvK is the guarantor.

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**Competing interests** AHvK reports grants from the Netherlands Organization for Health Research and Development (ZonMW) during the conduct of the study. No other disclosures were reported.

**Patient consent for publication** Not required.

**Ethics approval** This study involves human participants and was approved by the Ethics Committee of the Academic Medical Center in Amsterdam, the Netherlands (reference number: 2010\_297) and the local Ethics Committee of each participating hospital. Written informed consent was obtained from both parents before randomisation.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** Data are available upon reasonable request. Deidentified individual participant data (including data dictionaries) will be made available, in addition to study protocol, the statistical analysis plan and the analytical code. The data will be made available upon publication to researchers who provide a methodologically sound proposal for use in achieving the goals of the approved proposal. Proposals should be submitted to Professor Anton van Kaam (email: a.h.vankaam@amsterdamumc.nl).

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## Online supplementary content

**eTable 1.** Absolute risk differences for subgroup analyses of the composite outcome and its components at two years' corrected age.

**eTable 2.** Effect sizes of the differences in treatment effects between subgroups (i.e. treatment-by-subgroup interaction effect): ratio of odds ratios and difference of absolute risk differences, hydrocortisone vs. placebo, with corresponding confidence intervals and P value.

**eTable 3.** Sensitivity analysis: impact of  $r1$  and  $r2$  on the key long term composite outcome (death or neurodevelopmental impairment at two years' corrected age).

**eFigure 1.** STEPP plots of the heterogeneity of hydrocortisone versus placebo treatment effect by gestational age (A), respiratory index (B) and predicted probability of moderate/severe BPD or death (C) on the long-term composite outcome death or neurodevelopmental impairment (NDI) at two years' corrected age based on crude absolute risk difference estimates.

**eFigure 2.** STEPP plot of the heterogeneity of hydrocortisone versus placebo treatment effect by gestational age (A), respiratory index (B) and predicted probability of moderate/severe BPD or death (C) on the component death at two years' corrected age based on crude odds ratio and absolute risk difference estimates.

**eFigure 3.** STEPP plot of the heterogeneity of hydrocortisone versus placebo treatment effect by gestational age (A), respiratory index (B) and predicted probability of moderate/severe BPD or death (C) on the component neurodevelopmental impairment (NDI) at two years' corrected age based on crude odds ratio and absolute risk difference estimates.

## Original protocol and amendments SToP-BPD study

**Supplement to Statistical Analysis Plan – SAP for the long-term outcomes at two years' corrected age of the SToP-BPD study**

**eTable 1.** Absolute risk differences for subgroup analyses of the composite outcome and its components at two years' corrected age.

	Hydrocortisone	Placebo	Difference, % (95% CI)	P value for interaction test <sup>a</sup>
<b>Composite outcome death or NDI</b>				
Overall	97/171 (56.7)	116/185 (62.7)	-6.0 (-16.0 to 4.2)	NA
Subgroups				
Gestational age < 27 weeks	77/141 (54.6)	102/154 (66.2)	-11.6 (-22.4 to -0.5)	0.02
Gestational age ≥ 27 weeks	20/30 (66.7)	14/31 (45.2)	21.5 (-3.2 to 42.8)	
Small for gestational age: yes	18/24 (75.0)	29/37 (78.4)	-3.4 (-25.8 to 16.9)	0.89
Small for gestational age: no	79/147 (53.7)	87/148 (58.8)	-5.0 (-16.1 to 6.2)	
Respiratory index: ≤ median	36/70 (51.4)	58/102 (56.9)	-5.4 (-20.1 to 9.5)	0.70
Respiratory index: > median	61/101 (60.4)	58/83 (69.9)	-9.5 (-22.6 to 4.4)	
Male	53/89 (59.6)	63/105 (60.0)	-0.4 (-14.1 to 13.1)	0.24
Female	44/82 (53.7)	53/80 (66.3)	-12.6 (-26.8 to 2.5)	
Multiple birth	34/66 (51.5)	30/51 (58.8)	-7.3 (-24.4 to 10.6)	0.78
Singleton	63/105 (60.0)	86/134 (64.2)	-4.2 (-16.4 to 8.0)	
<b>Component death at 2 years' CA</b>				
Overall	39/181 (21.5)	56/190 (29.5)	-7.9 (-16.6 to 1.0)	NA
Subgroups				
Gestational age < 27 weeks	30/149 (20.1)	51/159 (32.1)	-11.9 (-21.4 to -2.1)	0.04
Gestational age ≥ 27 weeks	9/32 (28.1)	5/31 (16.1)	12.0 (-8.8 to 31.5)	
Small for gestational age: yes	8/26 (30.8)	18/38 (47.4)	-16.6 (-37.6 to 7.7)	0.37
Small for gestational age: no	31/155 (20.0)	38/152 (25.0)	-5.0 (-14.3 to 4.4)	
Respiratory index: ≤ median	10/77 (13.0)	29/104 (27.9)	-14.9 (-25.8 to -2.8)	0.20
Respiratory index: > median	29/104 (27.9)	27/86 (31.4)	-3.5 (-16.5 to 9.3)	
Male	21/95 (22.1)	28/109 (25.7)	-3.6 (-15.0 to 8.3)	0.27
Female	18/86 (20.9)	28/81 (34.6)	-13.6 (-26.7 to -0.07)	
Multiple birth	14/70 (20.0)	16/54 (29.6)	-9.6 (-24.9 to 5.4)	0.78
Singleton	25/111 (22.5)	40/136 (29.4)	-6.9 (-17.5 to 4.2)	
<b>Component NDI at 2 years' CA</b>				
Overall	58/132 (43.9)	60/129 (46.5)	-2.6 (-14.4 to 9.4)	NA
Subgroups				
Gestational age < 27 weeks	47/111 (42.3)	51/103 (49.5)	-7.2 (-20.1 to 6.1)	0.12
Gestational age ≥ 27 weeks	11/21 (52.4)	9/26 (34.6)	17.8 (-9.9 to 42.3)	
Small for gestational age: yes	10/16 (62.5)	11/19 (57.9)	4.6 (-25.9 to 33.4)	0.66
Small for gestational age: no	48/116 (41.4)	49/110 (44.5)	-3.2 (-15.8 to 9.6)	
Respiratory index: ≤ median	26/60 (43.3)	29/73 (39.7)	3.6 (-12.8 to 19.9)	0.24
Respiratory index: > median	32/72 (44.4)	31/56 (55.4)	-10.9 (-27.3 to 6.4)	
Male	32/68 (47.1)	35/77 (45.5)	1.6 (-14.3 to 17.4)	0.47
Female	26/64 (40.6)	25/52 (48.1)	-7.5 (-24.8 to 10.4)	
Multiple birth	20/52 (38.5)	14/35 (40.0)	-1.5 (-21.9 to 18.3)	0.99
Singleton	38/80 (47.5)	46/94 (48.9)	-1.4 (-16.0 to 13.2)	

Data are n (%) unless stated differently. CI=confidence interval, NA=not applicable, NDI=neurodevelopmental impairment, CA=corrected age.

<sup>a</sup> Subgroup analyses were performed and statistically tested with interaction effect of the specific subgroup and treatment in Generalized Linear Models with identity link function and binomial distribution, P-value for interaction is reported.

**eTable 2.** Effect sizes of the differences in treatment effects between subgroups (i.e. treatment-by-subgroup interaction effect): ratio of odds ratios and difference of absolute risk differences, hydrocortisone vs. placebo, with corresponding confidence intervals and P value.

	Ratio of odds ratio's, (95% CI)	P value for interaction test <sup>a</sup>	Difference of absolute risk differences, % (95% CI)	P value for interaction test <sup>b</sup>
<b>Composite outcome death or NDI</b>				
Subgroups				
Gestational age (< vs. ≥ 27 weeks)	0.25 (0.08 to 0.79)	0.02	-33.1 (-59.9 to -6.4)	0.02
Small for gestational age (yes vs. no)	1.02 (0.28 to 3.71)	0.98	1.7 (-22.9 to 26.2)	0.89
Respiratory index (≤ vs. > median)	1.22 (0.52 to 2.91)	0.65	4.0 (-16.4 to 24.5)	0.70
Sex (female vs. male)	0.60 (0.26 to 1.42)	0.24	-12.1 (-32.5 to 8.2)	0.24
Multiple pregnancy (singleton vs. multiple birth)	1.13 (0.46 to 2.79)	0.80	3.1 (-18.8 to 25.1)	0.78
<b>Component death at 2 years' CA</b>				
Subgroups				
Gestational age (< vs. ≥ 27 weeks)	0.26 (0.07 to 0.997)	0.049	-23.9 (-46.4 to -1.5)	0.04
Small for gestational age (yes vs. no)	0.66 (0.20 to 2.14)	0.49	-11.6 (-37.2 to 14.0)	0.37
Respiratory index (≤ vs. > median)	0.46 (0.17 to 1.25)	0.13	-11.4 (-28.7 to 6.0)	0.20
Sex (female vs. male)	0.61 (0.24 to 1.58)	0.31	-10.1 (-27.9 to 7.8)	0.27
Multiple pregnancy (singleton vs. multiple birth)	1.18 (0.43 to 3.22)	0.75	2.7 (-16.1 to 21.6)	0.78
<b>Component NDI at 2 years' CA</b>				
Subgroups				
Gestational age (< vs. ≥ 27 weeks)	0.36 (0.10 to 1.32)	0.12	-24.9 (-56.1 to 6.2)	0.12
Small for gestational age (yes vs. no)	1.38 (0.32 to 5.94)	0.67	7.8 (-27.2 to 42.7)	0.66
Respiratory index (≤ vs. > median)	1.80 (0.67 to 4.83)	0.24	14.5 (-9.7 to 38.7)	0.24
Sex (female vs. male)	0.69 (0.26 to 1.86)	0.47	-9.1 (-33.4 to 15.3)	0.47
Multiple pregnancy (singleton vs. multiple birth)	1.01 (0.35 to 2.91)	0.99	0.1 (-25.6 to 25.8)	0.99

CA=corrected age, CI=confidence interval, NDI=neurodevelopmental impairment

<sup>a</sup> Subgroup analyses were performed and statistically tested with interaction effect of the specific subgroup and treatment in logistic regression models, P-value for interaction is reported.

<sup>b</sup> Subgroup analyses were performed and statistically tested with interaction effect of the specific subgroup and treatment in Generalized Linear Models with identity link function and binomial distribution, P-value for interaction is reported.

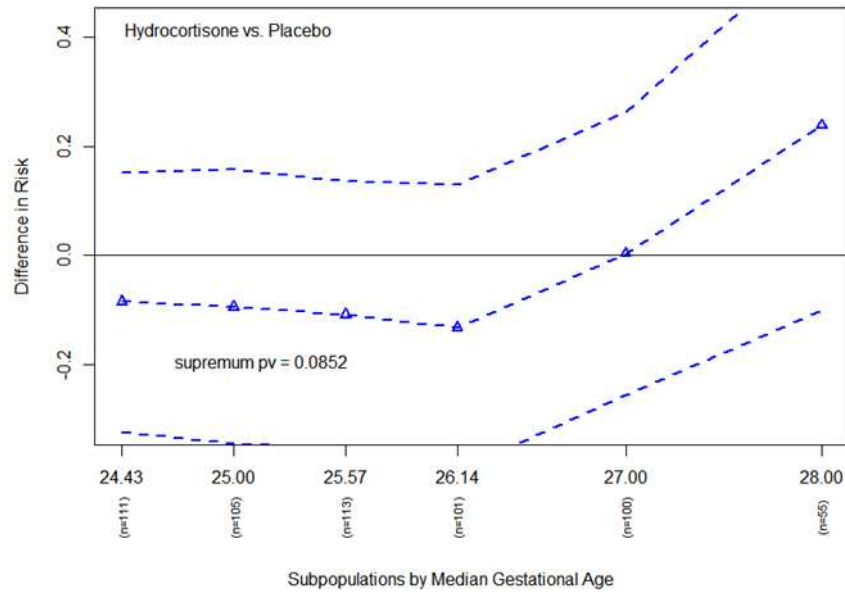
**eTable 3.** Sensitivity analysis: impact of  $r1$  and  $r2$  on the key long term composite outcome (death or neurodevelopmental impairment at two years' corrected age).

Candidate treatment effect modifier	$r2$	$r1$	$r1/r2$	# of subpopulations	Supremum P-value based on odds ratio estimates	Supremum P-value based on absolute risk difference estimates
<b>Gestational age</b>						
	100	30	30%	5	0.632	0.422
		50	50%	6	0.113	0.085
		70	70%	8	0.445	0.386
	80	24	30%	5	0.248	0.208
		40	50%	7	0.346	0.309
		56	70%	9	0.327	0.251
<b>Respiratory index</b>						
	100	30	30%	5	0.194	0.227
		50	50%	6	0.534	0.605
		70	70%	9	0.044	0.175
	80	24	30%	6	0.087	0.212
		40	50%	8	0.253	0.506
		56	70%	12	0.129	0.263
<b>Predicted probability of moderate/severe BPD or death</b>						
	100	30	30%	5	0.256	0.215
		50	50%	7	0.300	0.241
		70	70%	10	0.108	0.126
	80	24	30%	6	0.147	0.104
		40	50%	8	0.161	0.114
		56	70%	13	0.238	0.173

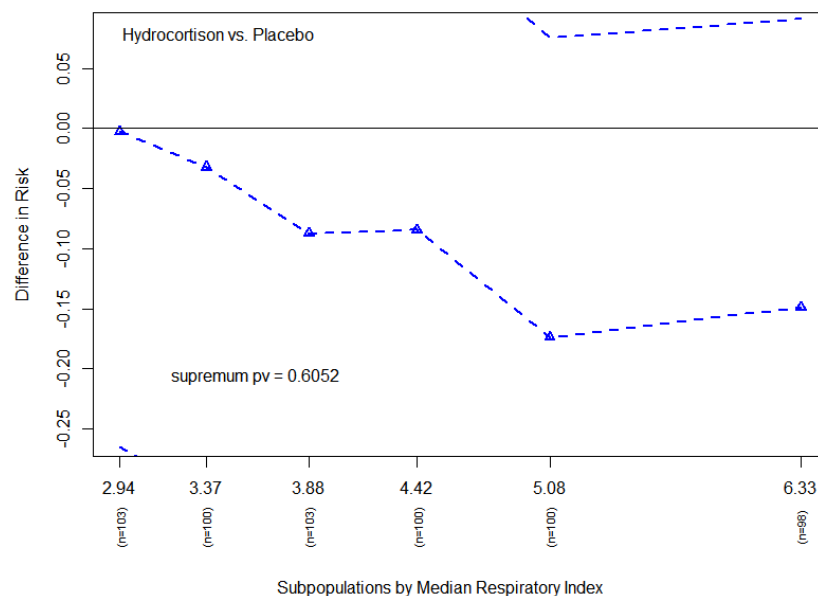
BPD=bronchopulmonary dysplasia.

**eFigure 1.** STEPP plots of the heterogeneity of hydrocortisone versus placebo treatment effect by gestational age (A), respiratory index (B) and predicted probability of moderate/severe BPD or death (C) on the long-term composite outcome death or neurodevelopmental impairment (NDI) at two years' corrected age based on crude absolute risk difference estimates.

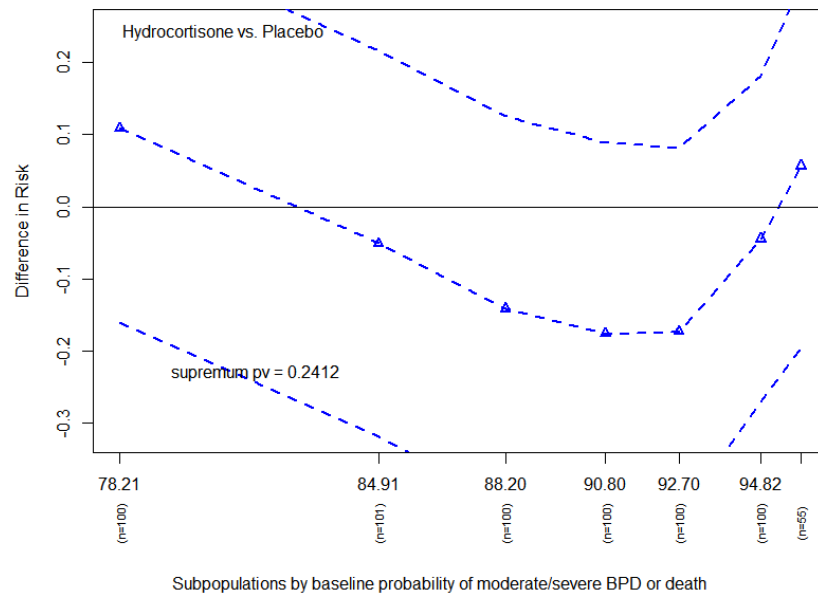
**A.** Composite outcome death or NDI by gestational age.



**B.** Composite outcome death or NDI by respiratory index.



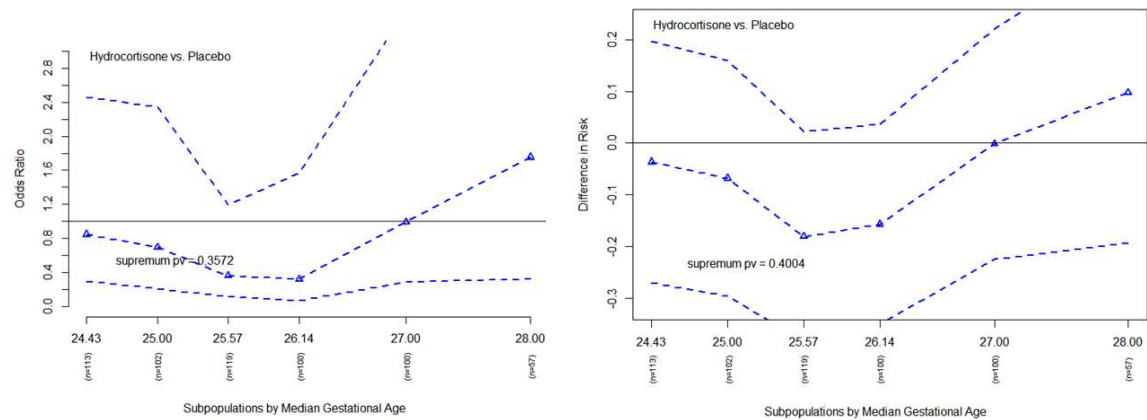
## C. Composite outcome death or NDI by predicted probability of moderate/severe BPD or death.



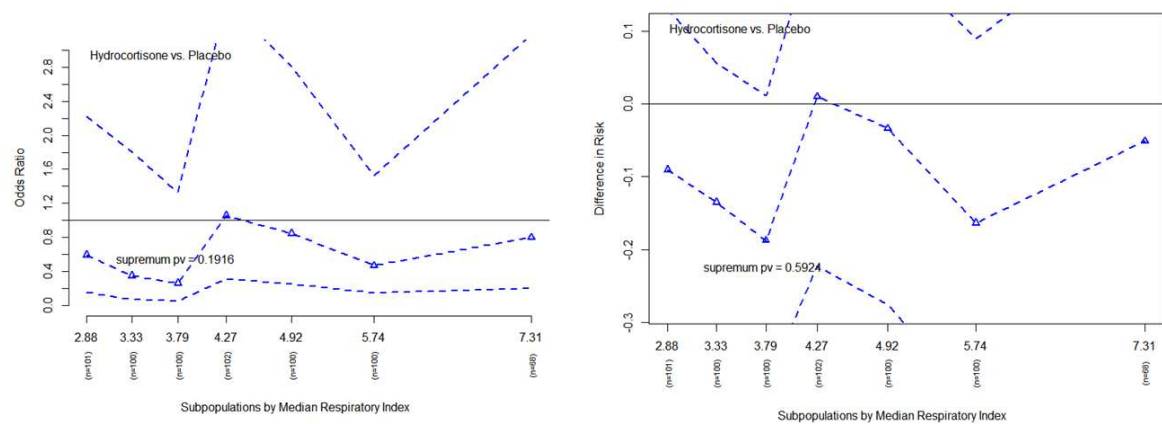
Subpopulations were chosen with sample size  $r2$  of 100 infants per subset and overlap  $r1$  of 50 infants between subsequent subsets. Shown are pointwise estimates and 95% confidence intervals of the absolute risk difference per subpopulation, plotted at the median value of the corresponding subpopulation. Interaction  $p$  values derived from permutations tests with 2500 resampling steps. A risk difference  $< 0$  indicates that hydrocortisone is the preferred strategy.

**eFigure 2.** STEPP plot of the heterogeneity of hydrocortisone versus placebo treatment effect by gestational age (A), respiratory index (B) and predicted probability of moderate/severe BPD or death (C) on the component death at two years' corrected age based on crude odds ratio and absolute risk difference estimates.

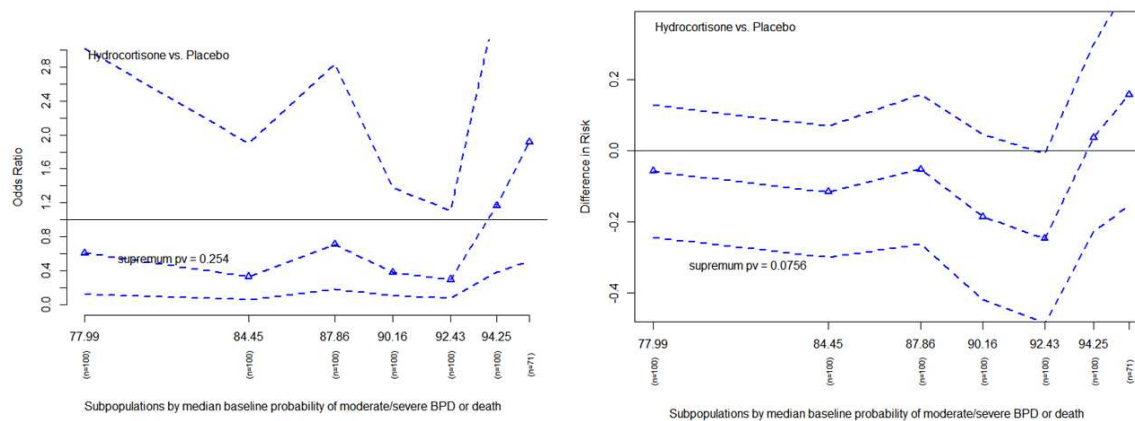
**A. Component death by gestational age.**



**B. Component death by respiratory index.**



C. Component death by predicted probability of moderate/severe BPD or death.

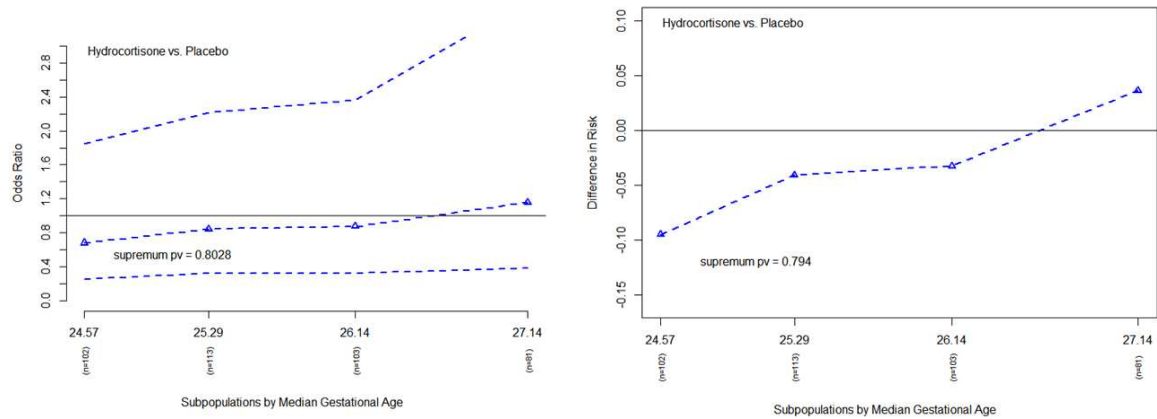


Subpopulations were chosen with sample size  $r2$  of 100 infants per subset and overlap  $r1$  of 50 infants between subsequent subsets. Shown are pointwise estimates and 95% confidence intervals of the odds ratio and absolute risk difference per subpopulation, plotted at the median value of the corresponding subpopulation. Interaction  $p$  values derived from permutations tests with 2500 resampling steps. An odds ratio  $< 1$  indicates that hydrocortisone is the preferred strategy; an absolute risk difference  $< 0$  indicates that hydrocortisone is the preferred strategy.

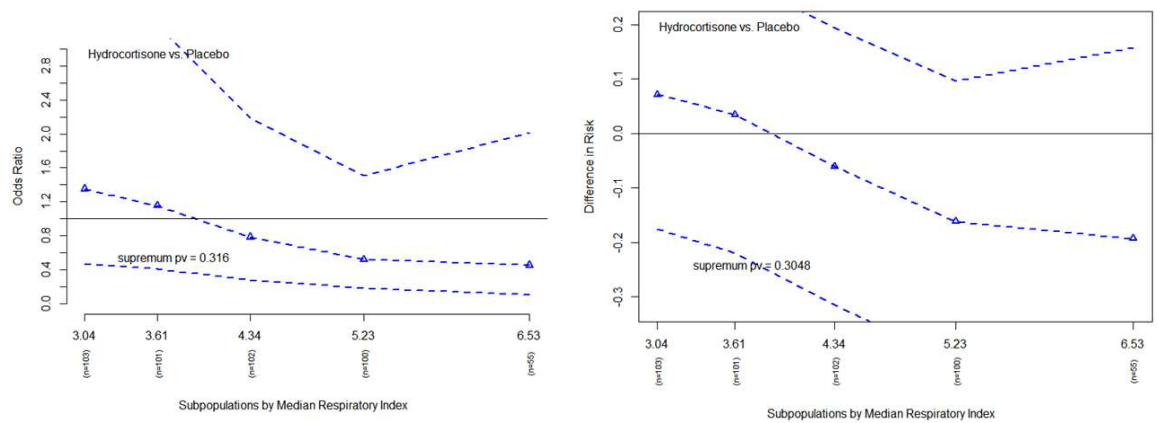


**eFigure 3.** STEPP plot of the heterogeneity of hydrocortisone versus placebo treatment effect by gestational age (A), respiratory index (B) and predicted probability of moderate/severe BPD or death (C) on the component neurodevelopmental impairment (NDI) at two years' corrected age based on crude odds ratio and absolute risk difference estimates.

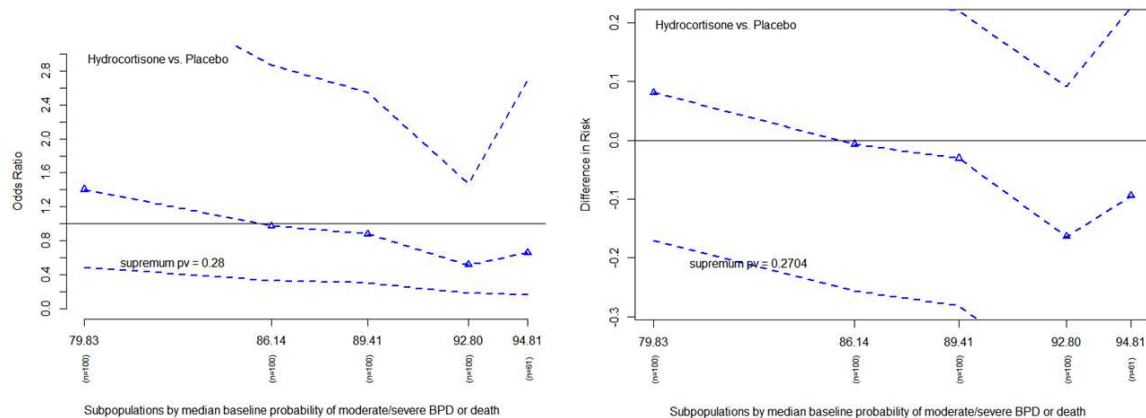
**A.** Component NDI by gestational age.



**B.** Component NDI by respiratory index.



C. Component NDI by predicted probability of moderate/severe BPD or death.



Subpopulations were chosen with sample size  $r2$  of 100 infants per subset and overlap  $r1$  of 50 infants between subsequent subsets. Shown are pointwise estimates and 95% confidence intervals of the odds ratio and absolute risk difference per subpopulation, plotted at the median value of the corresponding subpopulation. Interaction  $p$  values derived from permutations tests with 2500 resampling steps. An odds ratio  $< 1$  indicates that hydrocortisone is the preferred strategy; an absolute risk difference  $< 0$  indicates that hydrocortisone is the preferred strategy.

## 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**

<b>Protocol ID</b>	Systemic Hydrocortisone To Prevent Bronchopulmonary Dysplasia in preterm infants: the SToP-BPD study
<b>Short title</b>	<b>SToP-BPD Study</b>
<b>Version</b>	1
<b>Date</b>	18 november 2010
<b>Principal investigator</b>	<b>Anton van Kaam</b> 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 href="mailto:a.h.vankaam@amc.uva.nl">a.h.vankaam@amc.uva.nl</a>
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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%.<sup>1,2</sup> 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 life<sup>3</sup> and life-long  
201 alterations in lung function.<sup>4-6</sup> 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.<sup>7-9</sup> Furthermore, BPD is considered an important risk factor for adverse  
204 neurodevelopmental outcome after premature birth<sup>10-14</sup> with life-long economic and social  
205 consequences.<sup>15-18</sup>

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.<sup>19-21</sup> 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.<sup>22-24</sup>

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.<sup>25,26</sup> 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.<sup>27-29</sup> 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.<sup>30,31</sup>  
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.<sup>32-34</sup> 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 3<sup>rd</sup> or 4<sup>th</sup> week of life.<sup>27</sup>  
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.<sup>35</sup>  
231 However, no placebo controlled RCT has investigated the use of hydrocortisone after the  
232 first week in life in ventilator dependent preterm infants.<sup>36</sup> 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.<sup>37-42</sup> Only one of these trials reported long-term  
235 follow-up, showing no differences in adverse neurodevelopmental sequelae.<sup>43</sup> These  
236 findings are supported by several historical cohort studies, showing no increased risk of  
237 adverse neurodevelopmental outcome in hydrocortisone treated infants.<sup>44-46</sup>  
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.<sup>47</sup> 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.<sup>45,48</sup> 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.<sup>48</sup>  
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 FiO<sub>2</sub>) of ≥ 3.5 for more than 12 h/day for at least 48
- 305 hours, ensuring normal oxygen saturation (86-94%) and pCO<sub>2</sub> 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.<sup>24</sup> 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 trials<sup>26</sup>, 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.<sup>21</sup>, since the severity of BPD has a high association with neurodevelopmental  
451 sequelae.<sup>12</sup> 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.<sup>21,49,50</sup> 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.<sup>51</sup>
- 480 • retinopathy of prematurity, including grading following international classification<sup>52</sup>
- 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 Helsinki<sup>53</sup> 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.

765

766

767

768

769

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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.			

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946 Opmerkingen: [Klik hier en typ opmerkingen]

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949 sein: [Klik hier en typ seinnummer]

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956 **APPENDIX 2**

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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  $\text{SpO}_2$ . The diagnosis moderate BPD can be rejected when the  $\text{SpO}_2$  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,  $\text{SpO}_2$ , 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  $\text{SpO}_2$  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**

<b>Protocol ID</b>	Systemic Hydrocortisone To Prevent Bronchopulmonary Dysplasia in preterm infants: the SToP-BPD study
<b>Short title</b>	<b>SToP-BPD Study</b>
<b>Version</b>	2
<b>Date</b>	05 January 2011
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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%.<sup>1,2</sup> 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 life<sup>3</sup> and life-long  
1211 alterations in lung function.<sup>4-6</sup> 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.<sup>7-9</sup> Furthermore, BPD is considered an important risk factor for adverse  
1214 neurodevelopmental outcome after premature birth<sup>10-14</sup> with life-long economic and social  
1215 consequences.<sup>15-18</sup>

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.<sup>19-21</sup> 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.<sup>22-24</sup>

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.<sup>25,26</sup> 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.<sup>27-29</sup> 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.<sup>30,31</sup>  
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.<sup>32-34</sup> 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 3<sup>rd</sup> or 4<sup>th</sup> week of life.<sup>27</sup>  
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.<sup>35</sup>  
1241 However, no placebo controlled RCT has investigated the use of hydrocortisone after the  
1242 first week in life in ventilator dependent preterm infants.<sup>36</sup> 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.<sup>37-42</sup> Only one of these trials reported long-term  
1245 follow-up, showing no differences in adverse neurodevelopmental sequelae.<sup>43</sup> These  
1246 findings are supported by several historical cohort studies, showing no increased risk of  
1247 adverse neurodevelopmental outcome in hydrocortisone treated infants.<sup>44-46</sup>  
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.<sup>47</sup> 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.<sup>45,48</sup> 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.<sup>48</sup>  
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 FiO<sub>2</sub>) of  $\geq 3.5$  for more than 12 h/day for at least 48  
1322 hours, ensuring normal oxygen saturation (86-94%) and pCO<sub>2</sub> 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.<sup>24</sup> 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 trials<sup>26</sup>, 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.<sup>21</sup>, since the severity of BPD has a high association with neurodevelopmental

1467 sequelae.<sup>12</sup> 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.<sup>21,49,50</sup> 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.<sup>51</sup>
- 1496 • retinopathy of prematurity, including grading following international classification<sup>52</sup>



- 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 Helsinki<sup>53</sup> 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.

1781

1782

1783

1784

1785

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

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1973 **APPENDIX 2**

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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  $\text{SpO}_2$ . The diagnosis moderate BPD can be rejected when the  $\text{SpO}_2$  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,  $\text{SpO}_2$ , 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  $\text{SpO}_2$  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**

<b>Protocol ID</b>	Systemic Hydrocortisone To Prevent Bronchopulmonary Dysplasia in preterm infants: the SToP-BPD study
<b>Short title</b>	<b>Hydrocortisone for bronchopulmonary dysplasia</b>
<b>Version</b>	3
<b>Date</b>	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%.<sup>1,2</sup> 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 life<sup>3</sup> and life-long  
2232 alterations in lung function.<sup>4-6</sup> 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.<sup>7-9</sup> Furthermore, BPD is considered an important risk factor for adverse  
2235 neurodevelopmental outcome after premature birth<sup>10-14</sup> with life-long economic and social  
2236 consequences.<sup>15-18</sup>

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.<sup>19-21</sup> 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.<sup>22-24</sup>

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.<sup>25,26</sup> 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.<sup>27-29</sup> 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.<sup>30,31</sup>  
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.<sup>32-34</sup> 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 3<sup>rd</sup> or 4<sup>th</sup> week of life.<sup>27</sup>  
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.<sup>35</sup>  
2262 However, no placebo controlled RCT has investigated the use of hydrocortisone after the  
2263 first week in life in ventilator dependent preterm infants.<sup>36</sup> 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.<sup>37-42</sup> Only one of these trials reported long-term  
2266 follow-up, showing no differences in adverse neurodevelopmental sequelae.<sup>43</sup> These  
2267 findings are supported by several historical cohort studies, showing no increased risk of  
2268 adverse neurodevelopmental outcome in hydrocortisone treated infants.<sup>44-46</sup>  
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.<sup>47</sup> 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.<sup>45,48</sup> 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.<sup>48</sup>  
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 FiO<sub>2</sub>) of  $\geq 3.5$  for more than 12 h/day for at least  
2344 48 hours, ensuring adequate oxygen saturation (85-95%) and pCO<sub>2</sub> values in  
2345 premature infants (5.0-7.5 kPa).

2346 Note: these targets are used to ensure homogeneous assessment of MAwP and FiO<sub>2</sub> 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.<sup>24</sup> 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 trials<sup>26</sup>, 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 FiO<sub>2</sub>) 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.<sup>35</sup>*

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.<sup>37-42</sup> Only one of these trials reported long-term*  
2523 *follow-up, showing no differences in adverse neurodevelopmental sequelae.<sup>43</sup> 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.<sup>44-46</sup>*

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.<sup>45,48</sup> 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.<sup>48</sup> 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.<sup>21</sup>, since the severity of BPD has a high association with neurodevelopmental  
2626 sequelae.<sup>12</sup> 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.<sup>21,49,50</sup> 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.<sup>51</sup>
- 2655 • retinopathy of prematurity, including grading following international classification<sup>52</sup>
- 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.<sup>1,2</sup> 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.<sup>53,54</sup>*

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 Helsinki<sup>55</sup> 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.

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**APPENDIX 1 STUDIE MEDICATIE SCHEMA**

<b>Step 1: Fill in patient data in yellow cubicles. Use weight at day of randomization.</b>		<b>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</b>		<b>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.</b>		<b>Step 4: For print out of study medication list, press: <input type="button" value="Print"/></b>	
<b>Study identification</b>		<b>First administration</b>					
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	8-01-00 8:00	0.00 mg.	8-01-00 16:00																																	
Day 2	1-01-00 0:00	4 x	8-01-00 8:00	3 x	9-01-00 0:00		0.00 mg.	9-01-00 8:00																																							
	1-01-00 6:00		9-01-00 16:00																																												
	1-01-00 12:00		Day 10		10-01-00 0:00	3 x		10-01-00 8:00	0.00 mg.	10-01-00 16:00																																					
1-01-00 18:00	Day 11	11-01-00 0:00		3 x	11-01-00 8:00		0.00 mg.	11-01-00 16:00																																							
Day 3		2-01-00 0:00			4 x			12-01-00 0:00		2 x	12-01-00 12:00	0.00 mg.	12-01-00 12:00																																		
		2-01-00 6:00	Day 4			13-01-00 0:00		2 x	13-01-00 12:00		0.00 mg.		14-01-00 0:00	2 x	14-01-00 12:00	0.00 mg.	15-01-00 0:00	2 x	15-01-00 12:00	0.00 mg.	16-01-00 0:00	2 x	16-01-00 12:00	0.00 mg.	17-01-00 0:00	1 x	17-01-00 0:00	0.00 mg.	17-01-00 12:00	1 x	18-01-00 0:00	1 x	18-01-00 0:00	0.00 mg.	19-01-00 0:00	1 x	19-01-00 0:00	0.00 mg.	20-01-00 0:00	1 x	20-01-00 0:00	0.00 mg.	21-01-00 0:00	1 x	21-01-00 0:00	0.00 mg.	22-01-00 0:00

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3146 **APPENDIX 2**

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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  $\text{SpO}_2$ . The diagnosis moderate BPD can be rejected when the  $\text{SpO}_2$  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,  $\text{SpO}_2$ , 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  $\text{SpO}_2$  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**

<b>Protocol ID</b>	Systemic Hydrocortisone To Prevent Bronchopulmonary Dysplasia in preterm infants: the SToP-BPD study
<b>Short title</b>	<b>Hydrocortisone for bronchopulmonary dysplasia</b>
<b>Version</b>	4
<b>Date</b>	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%.<sup>1,2</sup> 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 life<sup>3</sup> and life-long  
3407 alterations in lung function.<sup>4-6</sup> 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.<sup>7-9</sup> Furthermore, BPD is considered an important risk factor for adverse  
3410 neurodevelopmental outcome after premature birth<sup>10-14</sup> with life-long economic and social  
3411 consequences.<sup>15-18</sup>

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.<sup>19-21</sup> 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.<sup>22-24</sup>

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.<sup>25,26</sup> 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.<sup>27-29</sup> 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.<sup>30,31</sup>  
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.<sup>32-34</sup> 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 3<sup>rd</sup> or 4<sup>th</sup> week of life.<sup>27</sup>  
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.<sup>35</sup>  
3437 However, no placebo controlled RCT has investigated the use of hydrocortisone after the  
3438 first week in life in ventilator dependent preterm infants.<sup>36</sup> 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.<sup>37-42</sup> Only one of these trials reported long-term  
3441 follow-up, showing no differences in adverse neurodevelopmental sequelae.<sup>43</sup> These  
3442 findings are supported by several historical cohort studies, showing no increased risk of  
3443 adverse neurodevelopmental outcome in hydrocortisone treated infants.<sup>44-46</sup>  
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.<sup>47</sup> 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.<sup>45,48</sup> 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.<sup>48</sup>  
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 FiO<sub>2</sub>) of ≥ 3.0* for more than 12 h/day for at least  
3519 48 hours, ensuring adequate oxygen saturation (85-95%) and pCO<sub>2</sub> values in  
3520 premature infants (5.0-7.5 kPa).

3521 Note: these targets are used to ensure homogeneous assessment of MAwP and FiO<sub>2</sub> 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.<sup>24</sup> 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 trials<sup>26</sup>, 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 FiO<sub>2</sub>) 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 patient shows signs of adrenal insufficiency at any  
3686 time during a stressful event, 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.<sup>35</sup>

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.<sup>37-42</sup> Only one of these trials reported long-term  
3732 follow-up, showing no differences in adverse neurodevelopmental sequelae.<sup>43</sup> 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.<sup>44-46</sup>

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.<sup>45,48</sup> 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.<sup>48</sup>

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.<sup>21</sup>, since the severity of BPD has a high association with neurodevelopmental

3838 sequelae.<sup>12</sup> 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.<sup>21,49,50</sup> should be preformed. 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.<sup>51</sup>
- 3867 • retinopathy of prematurity, including grading following international classification<sup>52</sup>
- 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.<sup>1,2</sup> 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.<sup>53,54</sup>

### 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 Helsinki<sup>55</sup> 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.

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**APPENDIX 1 STUDIE MEDICATIE SCHEMA**

<b>Step 1: Fill in patient data in yellow cubicles. Use weight at day of randomization.</b>		<b>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</b>		<b>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.</b>		<b>Step 4: For print out of study medication list, press: <input type="button" value="Print"/></b>			
<b>Study identification</b>		<b>First administration</b>							
Name		Date/time							
Date of birth		Lowering dosage regimen							
Weight		gram		Date/time					
<b>Day in regimen</b>	<b>Time</b>	<b>Times per day</b>	<b>mg/dose</b>	<b>Daily dose/kg</b>	<b>Day in regimen</b>	<b>Time</b>	<b>Times per day</b>	<b>mg/dose</b>	<b>Daily dose/kg</b>
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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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  $\text{SpO}_2$ . The diagnosis moderate BPD can be rejected when the  $\text{SpO}_2$  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,  $\text{SpO}_2$ , 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  $\text{SpO}_2$  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**

<b>Protocol ID</b>	Systemic Hydrocortisone To Prevent Bronchopulmonary Dysplasia in preterm infants: the SToP-BPD study
<b>Short title</b>	<b>Hydrocortisone for bronchopulmonary dysplasia</b>
<b>Version</b>	5
<b>Date</b>	11 November 2012
<b>Principal investigator</b>	<b>Dr. A.H.L.C. van Kaam</b> 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 href="mailto:a.h.vankaam@amc.uva.nl">a.h.vankaam@amc.uva.nl</a>
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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%.<sup>1,2</sup> 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 life<sup>3</sup> and life-long  
4616 alterations in lung function.<sup>4-6</sup> 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.<sup>7-9</sup> Furthermore, BPD is considered an important risk factor for adverse  
4619 neurodevelopmental outcome after premature birth<sup>10-14</sup> with life-long economic and social  
4620 consequences.<sup>15-18</sup>

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.<sup>19-21</sup> 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.<sup>22-24</sup>

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.<sup>25,26</sup> 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.<sup>27-29</sup> 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.<sup>30,31</sup>  
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.<sup>32-34</sup> 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 3<sup>rd</sup> or 4<sup>th</sup> week of life.<sup>27</sup>  
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.<sup>35</sup>  
4646 However, no placebo controlled RCT has investigated the use of hydrocortisone after the  
4647 first week in life in ventilator dependent preterm infants.<sup>36</sup> 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.<sup>37-42</sup> Only one of these trials reported long-term  
4650 follow-up, showing no differences in adverse neurodevelopmental sequelae.<sup>43</sup> These  
4651 findings are supported by several historical cohort studies, showing no increased risk of  
4652 adverse neurodevelopmental outcome in hydrocortisone treated infants.<sup>44-46</sup>  
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.<sup>47</sup> 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.<sup>45,48</sup> 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.<sup>48</sup>  
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  $\geq 2.5$  for more than 12 h/day for at least  
4728 48 hours, ensuring adequate oxygen saturation (85-95%) and pCO<sub>2</sub> values in  
4729 premature infants (5.0-7.5 kPa).



4730 Note: these targets are used to ensure homogeneous assessment of MAwP and FiO<sub>2</sub> 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 know 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.<sup>24</sup> 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 trials<sup>26</sup>, 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 FiO<sub>2</sub>) 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.<sup>35</sup>

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.<sup>37-42</sup> Only one of these trials reported long-term  
4942 follow-up, showing no differences in adverse neurodevelopmental sequelae.<sup>43</sup> 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.<sup>44-46</sup>

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.<sup>45,48</sup> 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.<sup>48</sup>

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 regimen 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.<sup>21</sup>, since the severity of BPD has a high association with neurodevelopmental  
5048 sequelae.<sup>12</sup> 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.<sup>21,49,50</sup> 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.<sup>51</sup>
- 5077 • retinopathy of prematurity, including grading following international classification<sup>52</sup>
- 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.<sup>1,2</sup> 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.<sup>53,54</sup>

#### 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 Helsinki<sup>55</sup> 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**

<b>Step 1: Fill in patient data in yellow cubicles. Use weight at day of randomization.</b>		<b>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</b>		<b>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.</b>		<b>Step 4: For print out of study medication list, press: <input type="button" value="Print"/></b>			
<b>Study identification</b>		<b>First administration</b>							
Name		Date/time							
Date of birth		Lowering dosage regimen							
Weight		gram		Date/time					
<b>Day in regimen</b>	<b>Time</b>	<b>Times per day</b>	<b>mg/dose</b>	<b>Daily dose/kg</b>	<b>Day in regimen</b>	<b>Time</b>	<b>Times per day</b>	<b>mg/dose</b>	<b>Daily dose/kg</b>
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

5563

5564 **APPENDIX 2**

5565

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  $\text{SpO}_2$ . The diagnosis moderate BPD can be rejected when the  $\text{SpO}_2$  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,  $\text{SpO}_2$ , 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  $\text{SpO}_2$  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

## Statistical analysis plan (SAP)

For the long-term outcomes of 2 years corrected age of the SToP-BPD study

**Trial registration:** Netherlands Trial Register, NTR2768. Registered on 17 February 2011.

EudraCT, 2010-023777-19. Registered on 2 November 2010.

Version 1, 16 March 2020.

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**On behalf of the SToP-BPD study group, this SAP is signed and dated by:**

Name	Signature	Date
Principal Investigator A. van Kaam, principal investigator		16-3-2020

**Supplement:*****Statistical analysis of the long-term outcomes at 2 years corrected age of the SToP-BPD study.***

This supplement is an update of and should be read in conjunction with the previously published statistical analysis plan (SAP) of the SToP-BPD study (1). Its purpose is to elaborate the statistical analyses of the long-term outcomes at 2 years corrected age (CA). We based this supplement on previously published recommendations (2). This supplement was prepared, signed and dated before the database of the long-term follow-up data at 2 years CA was locked and before unblinding of the researchers, outcome assessors, healthcare providers and parents of the patients.

*Analysis***1. Outcome definitions***Key long-term secondary outcome*

The key long-term secondary outcome at 2 years CA is a composite of death or neurodevelopmental impairment (NDI) at 2 years CA. To comply with the currently, generally used definition of NDI, the classification criteria cerebral palsy, hearing and vision loss were added to our previous NDI definition based on Bayley scores solely (1). This results in NDI being defined as the presence of anyone of the following:

- a Bayley Scales of Infant and Toddler Development, Third Edition, Dutch version (BSID-III-NL) (3) or corrected (see section 2) BSID-II (4-6) cognitive or motor composite score below 85, or an estimated cognitive delay of more than 3 months (see section 6 below); *OR*
- cerebral palsy with a Gross Motor Function Classification System (GMFCS) of more than 2; *OR*
- hearing loss requiring hearing aids or deafness; *OR*
- severe visual loss (blind or abnormal (limited vision, but the ability to see anything)).



### *Other long-term secondary outcomes*

Other long-term secondary outcomes include both individual components of the composite key long-term secondary outcome (death, NDI at 2 years CA), survival to 2 years CA (time-to-event), BSID-III composite cognitive and composite motor scores, cerebral palsy and its severity using the GMFCS (7), hearing problems severity (i.e. normal (no hearing problems), mild abnormal (light hearing loss for which control or treatment), abnormal (neurosensory hearing loss (partially) corrected with hearing aid) and severely abnormal (neurosensory hearing loss, deafness)), visual loss severity (i.e. normal (no problems with sight), mild abnormal (treated by ophthalmologist/orthoptist for abbreviation (goggles) or strabismus/amblyopia), abnormal (limited vision, but the ability to see anything) and severely abnormal (blind)), behaviour problems assessed by the Child Behaviour Checklist (8), number of hospital readmissions since first discharge to home (especially for respiratory reasons, vaccinations, surgical operations and intensive care admission with mechanical ventilation), growth at 2 years CA (weight, length and head circumference), use of inhalation medication, number of antibiotics courses and number of steroid courses for asthmatic exacerbations during the last year, and use of (para)medical support during the 2 years follow up period.

## **2. Calculations or transformations used to derive any outcome from the original data.**

### *Bayley Scales of Infant and Toddler Development*

During the recruitment period of the study the BSID-III-NL was the instrument used for neurodevelopmental outcome assessment in most centers, whereas in some centers the BSID-II-NL or the American norms were still used. To compensate for discrepancies between the BSID-II-NL and the BSID-III-NL, 5 points to the cognitive composite score and 10 points to the motor composite score will be added to the BSID-II-NL, as described previously (4-6). If the BSID-III was used with the American norms, for comparison with the Dutch norms, 4 points will be subtracted from the

cognitive composite score based on the American norms. For the motor composite score no correction of the American score is necessary (9).

#### *Anthropometric measurements*

The anthropometric measurements (weight, length and head circumference) at 2 years CA will be expressed as a z score. The z score will be calculated by using the deviation from the mean value for the sex- and age-specific reference population, divided by the SD for the reference population. The z scores are generated using the Dutch reference growth charts specified for age and gender (10).

### **3. Statistical analysis**

The analyses will be performed according to the intention-to-treat principle, including all randomised patients, regardless of protocol deviations or use of open-label corticosteroids. Descriptive statistics will be used to summarize baseline characteristics and outcome parameters using the mean and standard deviation or the median and interquartile range for continuous, normally and non-normally distributed outcomes respectively. Categorical outcomes will be summarized using counts and percentages. Treatment effect estimates will be expressed in absolute and relative effect sizes, as appropriate. Statistical uncertainty will be expressed in 95% confidence intervals (CI); all analyses will be performed using 2-sided tests and  $P < .05$  are regarded as statistically significant. No adjustments for multiple comparisons will be made.

#### *Key long-term secondary composite outcome*

Statistical analysis of the key long-term secondary composite outcome, death or NDI at 2 years CA, will be performed similarly to the analysis of the short-term primary outcome (composite of death or BPD at 36 weeks' postmenstrual age) (1, 11). Crude estimates of the absolute risk difference and odds ratio for the key long-term secondary composite outcome of the hydrocortisone group compared with the placebo group will be calculated.

A logistic regression model correcting for the stratification factors gestational age and study center will be used to estimate the adjusted odds ratio for the key long-term secondary composite outcome. A generalized linear model with a binomial distribution and identity link will be used to estimate the absolute risk difference adjusted for the stratification factors for the key long-term secondary composite outcome.

#### *Other long-term secondary outcomes*

The effect of hydrocortisone compared with placebo on the other long-term secondary outcomes will be analysed using regression models, as appropriate. If required, non-normally distributed continuous variables will be appropriately transformed or a non-parametric alternative analysis approach, as appropriate, will be used instead. In case of less than 20 (non)events, Fisher's Exact test will be performed. Survival analysis up to 2 years CA will be performed using Kaplan-Meier curves and the log-rank test; time-to-event will be calculated as the time between randomisation and death, 2 years CA (censoring event), or in case of lost to follow up, date of last contact (censoring event), whichever occurs first; the effect size will be expressed in a crude hazard ratio if the proportionality assumption is met, which will be checked using graphical examination and use of a time-dependent covariate in a Cox model. These outcomes, although all pre-specified, should be considered exploratory, yielding hypothesis-generating findings, and so no formal adjustments for stratification or multiple comparisons will be made.

#### **4. Sensitivity analyses**

To check the robustness of the analysis of the key long-term secondary composite outcome, we will perform a per-protocol analysis, including only infants treated according to the study protocol. If possible, we will perform sensitivity analyses on the key long-term secondary composite outcome to investigate the impact of correlation between infant outcomes within twin or higher-order multiple births using generalized estimating equations with a logit link function. A mixed-effects logistic

regression model with site as random effect will be performed as an additional sensitivity analysis to check the robustness of the main analysis of the key long-term secondary composite outcome, if possible.

## 5. Subgroup analyses

We will perform exploratory subgroup analyses of the effect of hydrocortisone on the key long-term secondary composite outcome and its individual components by examining treatment × sub-group interaction effects in logistic regression models. Statistical tests for interaction directly examine the strength of evidence for the treatment effect varying between subgroups (12-14). Treatment effect estimates within each specific subgroup category with their corresponding 95% confidence interval will be reported (15), independently of whether the test of the specific interaction term is statistically significant. We will perform four subgroup analyses for both the key long-term secondary composite outcome and its individual NDI component at 2 years CA, each examining one sub-group: gestational age groups (less than versus greater or equal to 27 weeks), small for gestational age (defined as birth weight below the 10<sup>th</sup> percentile for the gestational age on the Fenton growth charts, yes versus no) (16), parental education (low versus middle and high educational level) (17, 18) and multilingual environment (mono- versus multilingual environment) (19). For the individual component death at 2 years CA, subgroup analyses will be performed conform the first phase of the trial: gestational age (less than versus greater or equal to 27 weeks), small for gestational age (yes versus no), the respiratory index (RI) at randomisation (less than or equal to versus greater than the median), sex (male versus female), and multiple birth (single versus multiple) (11). Each of these analyses will require four parameters to be estimated in the logistic regression model. If there are fewer than 40 patients with and/or fewer than 40 patients without the event of interest at 2 years CA, these analyses will not be performed.

## 6. Missing data

In case of missing data, every attempt will be undertaken to retrieve the data. Missing data will not be imputed, with the exception of the key long-term secondary composite outcome. Parents of participants who do not attend the 2-year assessment at the outpatient clinic will be invited by telephone once more. If they refuse to attend, the reason for refusal will be documented and they will be considered as lost to follow up. If no BSID III test can be done because of impairment or the cognitive composite score is missing, the attending pediatrician is asked to fill in an estimate of cognitive delay in three categories: no delay, 3-6 months delay or >6 months delay. A delay of  $\geq 3$  months is considered as neurodevelopmental impairment and equivalent to a BSID-III cognitive and motor composite score  $<85$ . If the motor part of the assessment is missing, the motor composite score is considered to be in the normal range (above 85), if the neurological examination of the participant is assessed as normal. In case of missing data for one of the other components of NDI, i.e. neurological examination, vision or hearing, a committee of three independent experts will assess whether the participant has neurodevelopmental impairment or not on the basis of the available clinical information of their neurological and developmental (ab)normality, if reasonably possible. These experts will be kept blinded to the allocation arm during this assessment. If there is insufficient information to classify the key long-term secondary composite outcome in  $> 5\%$  of the participants, missing outcomes will be imputed using multiple imputation using baseline characteristics. As previously recommended (20), we will obtain a number of imputed datasets equal to the percentage of missing data. These datasets will be combined using Rubin's rules (20, 21). Inspection and imputation of missing data will be performed during the blinded review of the data. This strategy will be updated if, during the blinded data review, unexpected patterns are detected, requiring an appropriately adapted handling procedure. In that case, relevant deviations will be clearly documented and justified. If multiple imputation is performed, additional sensitivity analyses will be performed to check the robustness of the results using complete cases only and by applying best case and worst case imputation scenarios.

## 7. Additional analyses

For the key long-term secondary composite outcome a multivariable logistic regression model will be performed including gestational age (<27/≥ 27 weeks), small for gestational age (defined as birth weight below the 10<sup>th</sup> percentile for the gestational age, yes/no) (16), parental education (low/middle and high education) and multilingualism (mono-/multilingual) (19). Parental educational level is defined as low if one or both parents have attended lower professional school or less or one parent low and the other middle; middle if both parents have attended medium professional school or one low and the other high; and high if one or both parents have attended higher professional school or university or one parent high and the other middle, as described previously (18). Because particularly lower parental education is predictive of cognitive impairment (17), the parental educational level of education is dichotomized (low/middle and high educational level).

Furthermore an additional multivariable logistic regression model will be performed to assess the treatment effect on death at 2 years CA, including gestational age, small for gestational age, severity of lung disease as measured by respiratory index, sex and multiple birth, conform the first phase of the trial (11).

## 8. How will harms be reported?

All clinically relevant serious adverse events occurring in the period between discharge home and follow up at 2 years CA are included in the outcomes of this study and will be presented and analysed as described above. Eventual other serious adverse events (SAEs) not listed in the outcomes, that may occur in the period between discharge home and the follow up at 2 years CA are out of view of the NICU clinicians and can mostly be considered as a consequence of childhood rather than related to the study intervention under evaluation. As approved by the accredited medical ethics committee these SAEs were not reported.

### **9. Statistical software**

All statistical analysis will be performed in IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp, Armonk, NY). If necessary, for statistical computing the R environment is used (R Foundation for Statistical Computing, Vienna, Austria).

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