Hydrocortisone treatment of cardiovascular insufficiency in term and late preterm infants: A randomized controlled trial

Short Title: Hydrocortisone for Cardiovascular Insufficiency
Clinical trials.gov: NCT01954056

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Version 1.1
February 24, 2014
Revised April 2, 2014

PROTOCOL REVIEW CHECKLIST

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1. Abstract

This study proposes to conduct a multicenter, randomized, masked, placebo-controlled trial within the Neonatal Research Network (NRN). This trial will evaluate the effects of a 7-day course of hydrocortisone therapy on short-term morbidity, cardiovascular function, long-term neurodevelopment, and mortality in critically ill, term and late preterm infants diagnosed with cardiovascular insufficiency as defined by a need for inotrope therapy in the first 72 hours of age.

2. Statement of the Problem

Cardiovascular insufficiency is common and potentially life-threatening in critically ill term and late preterm newborns admitted to the newborn intensive care unit (NICU) in the first few days of age. Cardiovascular insufficiency occurs when there is inadequate blood flow to meet the needs of metabolism and often presents as low blood pressure, poor capillary refill, low urine output, or metabolic acidosis. Critically ill infants with these signs often receive fluid boluses or inotropes and, increasingly, steroids to improve systemic blood flow. Yet, for the majority of infants, the etiology of cardiovascular insufficiency in the first few days of life is unclear. Emerging evidence suggests that a frequent etiology of cardiovascular instability or insufficiency in ill adult and some pediatric populations may be relative adrenal insufficiency, an inadequate cortisol response to acute stress or illness.[1-4] Glucocorticoid treatment in some critically ill populations results in decreased mortality and morbidity in some studies.[4-8]

Small studies have documented inappropriately low cortisol values in conjunction with cardiovascular dysfunction in critically ill term and late preterm newborn infants.[9-11,12-14] In addition, we have shown that such infants have low endogenous concentrations of adrenocorticotropic hormone (ACTH) and have normal responses to exogenous ACTH.[12] Although small case series and retrospective studies have documented improved cardiovascular stability following glucocorticoid treatment in hypotensive term infants,[13-17] no randomized controlled trials (RCTs) have evaluated the effects of glucocorticoids on cardiovascular function, short-term outcomes, or long-term neurodevelopment in critically ill term or late preterm infants with cardiovascular insufficiency. It is urgent that research is advanced in this area because, despite the lack of well-designed studies, there is an increasing use of glucocorticoid therapy for hypotension in this population. This study aims to determine, through optimal study design, the efficacy and consequences of glucocorticoid therapy in critically ill term and late preterm infants.

3. Hypothesis

We hypothesize that therapy with hydrocortisone will ameliorate the clinical syndrome of cardiovascular insufficiency syndrome seen in many critically ill term and late preterm infants, thereby decreasing short- and long-term morbidity and mortality.

4. Specific Aims

Goal of study. Although short term use of hydrocortisone is believed to be safe *(see Table 1),* evidence is limited to support its use in treating hypotension in the critically ill term and late preterm infant. **Despite this paucity of data, many infants are increasingly receiving glucocorticoids for cardiovascular insufficiency**—13.1% of intubated and mechanically ventilated infants in our own preliminary observational NRN data and 13.5% in a recent report of infants with meconium aspiration syndrome.[18] We propose to **perform a RCT of hydrocortisone** for the treatment of cardiovascular insufficiency in critically ill, term and late preterm newborn infants who are mechanically ventilated in their first 72 postnatal hours. Our

goal is to determine if hydrocortisone treatment improves cardiovascular function, ameliorates other short-term outcomes, and increases survival without neurodevelopmental impairment.

Specific aims of this multicenter, randomized, masked, placebo-controlled trial within the NRN are:

a. Compare the incidence of death or neurodevelopmental impairment at 22-26 months in critically ill, mechanically ventilated, term and late preterm newborn infants receiving inotropes for cardiovascular insufficiency in the first 72 hours of age treated with 7 days of hydrocortisone vs. placebo. We **hypothesize** that hydrocortisone will decrease the incidence of death or neurodevelopmental impairment in these infants compared to placebo.

b. Compare short-term outcomes between infants treated with hydrocortisone vs. placebo including duration of mechanical ventilation and oxygen therapy, days to full feeding, and length of hospital stay. We **hypothesize** that infants who receive hydrocortisone will spend fewer days on mechanical ventilation and oxygen, will take fewer days to reach full enteral feeds, and will have shorter stays in the hospital.

c. Compare adverse events (defined below) between infants treated with hydrocortisone vs. placebo. We **hypothesize** that adverse events will not occur at a higher rate in those receiving hydrocortisone compared to placebo.

d. Compare measures of cardiovascular sufficiency between those infants on hydrocortisone vs. placebo as measured by pre- and post-study drug differences in blood pressure, the duration and dose of inotropes received, and the presence of metabolic acidosis and oliguria. We **hypothesize** that infants treated with hydrocortisone vs. placebo will have higher blood pressures, receive a lower total dose of inotropes, and/or receive inotropes for a shorter period of time and have less metabolic acidosis and oliguria.

Table 1. Hydrocortisone dosing

Author	Year	N=	Population Gestational Age	Study Design	Entry Criteria	Hydrocortisone Dose and Duration Used	Results	Adverse Events
Seri[47]	2001	N=21	Mean: 26.9 wks	Retro-spective	Dopa ≥22 mcg/k/min	2 mg/kg/day div q12h for 1-3 days OR: 3-6 mg/kg/day div q12h OR: QID for 2-3 days	Increased blood pressure (BP), decreased fluid & pressor requirements	No events reported
Ng	2006	N=48	<32 weeks	RCT	Dopa ≥10 plus saline ≥30 cc/kg	3 mg/kg/day div q8h for 5 days	Increased BP, weaned off pressors faster, decreased fluid & pressor requirement	More glycosuria but no change in serum sugar. No change in rates of infection, necrotizing enterocolitis (NEC), SIP, duration of hospital stay or mortality.
Noori	2006	N=15	5 term, 15 preterm	Observation	Dopa ≥15	2 mg/kg once, then 2mg/kg/day div q12h	Increased BP, no change in stroke vol or cardiac	No change in middle cerebral or renal artery

Author	Year	N=	Population Gestational Age	Study Design	Entry Criteria	Hydrocortisone Dose and Duration Used	Results	Adverse Events
						for 2 days	output, decreased pressor need.	flow.
Baker	2008	N=117	Mean: 35 weeks	Observation	Inotrope >20 & cortisol <5 mcg/dl	3.3 mg/kg/day div q6h for 2 days, then 1.1 mg/kg/day div q6h, then weaned over median of 6 days	Increased BP, decreased pressor requirement & less oliguria	No difference intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), infection, SIP compared to controls. No correlation of cortisol to response to treatment.
Bourchier	1997	N=40	Preterm	RCT: hydrocortisone vs dopa	MAP <25 or 35 depending on weight	2.5mg/kg/ dose q6h for 2 days, then 1.25 mg/kg q6h for 2 days, then 0.625mg/kg for 2 days or dopa	No difference between dopa or hydrocortisone	No difference in mortality, IVH, retinopathy of prematurity, CLD, NEC, serum sugar, or sepsis.

5. Rationale/Justification

There has never been a randomized controlled trial of hydrocortisone for the treatment of cardiovascular insufficiency in term and late preterm newborn infants in the first few days of life. No studies have examined the long-term effects of hydrocortisone given for the purposes of improving cardiovascular stability. This RCT is urgently needed because the use of steroids is rapidly increasing in hypotensive critically ill term and late preterm infants without evaluation of efficacy or safety *(see also section 6b, Preliminary Studies, below).*[18,19] Investigators at the University of New Mexico Health Sciences Center have been performing investigations in the area of adrenal function and cardiovascular dysfunction in the critically ill term and late preterm infant since 2002 and most recently, within the multicenter NRN. The proposed study can only be conducted through a multicenter collaboration. The NRN is a well-established network of academic neonatal centers that has systems in place and extensive experience in conducting large trials. We have instituted a database for this particular targeted study population within the NRN and the investigators have experience in formulating, managing, and editing this database. In addition, the NRN has an established follow-up program with successful tracking of patients and high follow-up rates, standardized assessments conducted by certified examiners, and comprehensive data management.

6a. Background/Previous Studies

Incidence of cardiovascular insufficiency. Cardiovascular insufficiency is a frequent occurrence in the critically ill term and late preterm infant admitted to the NICU. Previous studies on cardiovascular insufficiency have used hypotension as a proxy measure of insufficiency, rather than other signs of cardiovascular insufficiency.[16,20-23] This may not be the most appropriate measure as many neonatal clinicians do not use blood pressure to determine initiation of therapy *(see section 6b, Preliminary Studies, below).* If hypotension is defined

pragmatically as the receipt of therapy for the diagnosis, one retrospective study of 1011 mechanically ventilated, ≥34 week neonates admitted to a NICU reported that 60% received volume expanders and 35% received vasopressors.[24]

Consequences of cardiovascular insufficiency. The consequences of cardiovascular insufficiency are the result of end organ injury or damage. In extremely preterm infants, hypotension has been associated with intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), cerebral palsy, hearing loss, and neurodevelopmental impairment.[25-27] It is difficult to differentiate the consequences of hypotension itself from the treatment, as treated blood pressure vs. untreated low blood pressure may be associated with adverse outcomes in retrospective, multiple regression analyses.[28,29]

Although less is known about the critically ill term or late preterm infant, there are reports of increased neurological events (seizures, brain atrophy, intracranial hemorrhage, or stroke) and chronic lung disease in association with the use of vasopressors (inotropes).[24] Other studies have reported a higher incidence of death in ill newborn infants who received vasopressors compared to those who did not (68.2% vs. 15.7%).[18] These adverse outcomes may have been due to the underlying disease, inadequate perfusion, vasopressor (inotrope) therapy, or other factors. It will remain difficult to sort out the contributions of these factors; however, a randomized, placebo-controlled trial is the best strategy to determine the efficacy and consequences of therapies given to maintain cardiovascular stability.

Adrenal insufficiency as etiology of cardiovascular insufficiency. The etiology of hypotension or cardiovascular insufficiency in the acutely ill newborn is, in most cases, unknown at the time of treatment. Proposed mechanisms include hypovolemia, myocardial dysfunction, abnormal regulation of peripheral vascular tone, pulmonary hypertension with resultant decreased left ventricular preload, and maladaptation to transition after birth.[30] Recently, studies have suggested relative adrenal insufficiency as an etiology of hypotension in other critically ill populations of adults and children.[2,31-34] Adrenal insufficiency occurs when there is insufficient cortisol release from the adrenal cortex, especially in response to severe illness and stress. The adrenal gland releases cortisol in response to ACTH. ACTH is produced in the pituitary gland, which is stimulated by corticotrophin-releasing hormone (CRH) that is made in the hypothalamus. The integrity and activation of the hypothalamic-pituitary-adrenal (HPA) axis is essential to general adaptation to illness and stress. The HPA axis is responsible for the maintenance of cellular and organ homeostasis. In response to acute stress or critical illness, cortisol concentrations should increase substantially. Recent guidelines for adults with critical illness have suggested that random cortisol values <10 mcg/dl or delta cortisol values <9 mcg/dl after cosyntropin is associated with cardiovascular insufficiency and mortality and should be considered evidence of relative adrenal insufficiency.[4-6,8,33,35]

There is **no consensus on the definition of relative adrenal insufficiency** in the acutely ill newborn infant because data regarding adrenal function in the ill newborn are sparse. Term newborns have demonstrated the ability to adapt quickly to postnatal changes and can show a response to stress by the end of the first postnatal week.[36] However, small studies, including our work,[12] have documented inappropriately low cortisol concentrations in sick, hypotensive term newborns during this first week.[11,16,37] In addition, one of these studies reported low cortisol responses to ACTH and a high mortality rate in such infants.[11] These studies suggest that insufficient adrenal function in the face of illness may play a role in the etiology of hypotension or cardiovascular insufficiency in the term and late preterm critically ill newborn infant.

We postulate that the **newborn is uniquely susceptible to adrenal insufficiency** due to shifts in hormone production during transition to extra-uterine life. CRH is produced in increasing concentrations by the placenta through gestation, resulting in maternal and fetal serum CRH

concentrations at term that are much higher than at any other time in life.[38] Placental CRH stimulates cortisol production in the fetal adrenal gland. At birth, the very high concentration of CRH from the placenta is suddenly withdrawn. We hypothesize that the pituitary gland of the newborn infant—who has previously been exposed to such high concentrations of CRH—is transiently refractory to the lower concentrations of CRH produced by the hypothalamus, and may not be able to increase ACTH to stimulate the adrenal gland for several days after delivery. If the newborn is well, this brief refractory period is well tolerated; however, if the infant is seriously ill, a state of relative adrenal insufficiency and cardiovascular compromise, including hypotension, may ensue. Our preliminary investigations have documented low cortisol and ACTH values in ill hypotensive newborns, but normal responses to exogenous ACTH, consistent with adrenal insufficiency secondary to HPA axis dysfunction upstream from the adrenal gland and poor adaptation to extra-uterine life.[12]

Glucocorticoid therapy for cardiovascular insufficiency. If relative adrenal insufficiency underlies the hypotension or cardiovascular insufficiency seen in many critically ill newborn infants, the appropriate therapy for this condition is not symptomatic treatment with volume expansion and inotropes, but **glucocorticoid therapy** in doses designed to mimic serum concentrations seen in critical illness. This approach is different than the goal of anti-inflammatory dosing of steroids (hydrocortisone or dexamethasone) used in preterm infants for the prevention of bronchopulmonary dysplasia. Glucocorticoids for the purpose of physiologic replacement in shock has shown to improve outcomes in adult critically ill patients, including a reduction in the duration of inotrope administration and, in some studies, reduced mortality.[4,8] Although no long-term outcomes have been studied, randomized controlled trials of glucocorticoids for the prevention and treatment of hypotension in preterm infants have shown an improvement in blood pressure.[20,21] Glucocorticoid administration for hypotension has not been associated with any adverse events in the small cohort or case studies in the term newborn population[14-16] and has not been shown to be an independent risk factor for adverse neurodevelopmental outcomes.[39]

Hydrocortisone dosing. High-dose corticosteroid administration has shown no benefit and possible harm in critically ill adult patients with acute lung injury, acute respiratory distress syndrome (ARDS), and septic shock.[40] Instead, prolonged, low-dose corticosteroid therapy has shown a beneficial effect on short-term mortality, ventilation-free days, length of intensive care unit stay, multiple organ dysfunction syndrome scores, lung injury scores, and shock reversal without increasing significant adverse events.[5,6,40] Relative adrenal insufficiency in ill adults—or more recently deemed "critical illness-related corticosteroid insufficiency"—is defined by catecholamine refractory shock (norepinephrine or equivalent dose of inotrope >0.05 to 0.1 mcg/kg/min) or having persistent ARDS for >48 hours. In these adult patients, a course of hydrocortisone at a dose of 200–350 mg/day (stress doses) is recommended, which is equivalent to at least 3 mg/k/day. The duration should be for at least 7 days because rapid steroid tapers (2–6 days) have been associated with rebound inflammation, increased inflammatory mediators, and a need to reintroduce vasopressor agents and mechanical ventilation.[41,42] The definition of relative adrenal insufficiency in adults is a random cortisol level below 10 or 15 mcg/dl in acutely ill patients. To achieve cortisol levels of 15–20 mcg/l, a dose of about 0.6 mg/kg/dose q 6 hours (~2.4 mg/kg/day) would need to be given.[43]

Hydrocortisone dosing in infants. Pharmacokinetic data in term and late preterm infants are limited. In 1962, Reynolds, *et al,* reported pharmacokinetics in five term infants after a bolus of 5 mg/kg hydrocortisone.[44] Serum concentrations were evaluated with two assay methods (Porter-Silber chromogen values and chromatography with isotope dilution), which showed similar results. Mean peak serum concentration (30–80 minutes after dose) was 557 mcg/dl, and mean serum half-life was just under 4 hours (range 2.4–7.1 hours). This half-life is much longer than in

adults, where elimination half-life has been reported to be 2 ± 0.3 hours.[45] Extrapolating, a dose of 0.5 mg/kg would give a peak cortisol level of approximately 50 mcg/dl or a level of about 18 mcg/dl after 6 hours.

Doses as low as 1 mg/kg/day in preterm infants have been shown to significantly increase blood pressure.[46] Studies of vasopressor-dependent, critically ill term and preterm newborn infants have used variable dosing (2–3 mg/kg/day), and all have shown an increase in blood pressure, a decrease in volume and inotrope requirement, and a decrease in heart rate without increases in adverse events *(see Table 1).*

Considering the likely longer $T^{1/2}$ for newborn infants and the biological effect, a dose of 1 mg/kg/dose load followed by 0.5 mg/kg q 6 hours is a reasonable initial dosing strategy.

6b. Preliminary Studies

We have been performing investigations in the area of adrenal function and cardiovascular dysfunction in the critically ill term and late preterm infant at the University of New Mexico Health Sciences Center since 2002 and most recently, within the multicenter NRN.

To determine the incidence of low cortisol values in infants receiving vasopressors, as evidence of cardiovascular insufficiency, we performed a **retrospective cohort study** of infants ≥35 weeks gestational age (GA) and who were mechanically ventilated, received vasopressor therapy, and had a cortisol concentration obtained for evaluation of vasopressor-resistant hypotension. **We found that a significant number (56%) of hypotensive critically ill infants** had cortisol values <15 mcg/dl, a value considered to be **suggestive of relative adrenal insufficiency**.[35] Treatment with hydrocortisone in this population resulted in improved hemodynamic function, as evidenced by decreased heart rate, decreased dopamine support, and fewer fluid boluses.

In a subsequent prospective observational study, we enrolled a cohort of mechanically ventilated infants ≥35 weeks gestation and <6 days old. Twenty-six of the 35 ill infants (**74%**) had cortisol levels <15 mcg/dl. However, all ACTH-stimulated cortisol values were >18 mcg/dl. We performed ACTH measurements in 10 infants; the median ACTH concentration was 12 pg/ml. There was no correlation between severity of illness scores and any cortisol value (baseline, stimulated, or rise). The results confirmed that the ***majority of critically ill newborns had an <u>inadequate</u> cortisol response to acute illness. Cortisol values did not increase with severity of illness***, again suggesting relative adrenal insufficiency. However, ***these infants did respond appropriately to ACTH stimulation, despite having lower ACTH values than expected for the degree of illness.***[11,47] *This suggests that their inadequate response to acute illness was not due to inadequate adrenal capacity to produce and secrete cortisol****, but to dysfunction of a different component of the HPA axis***.

To determine the best design for an RCT that examines the benefits and safety of hydrocortisone in this population, we first needed **to better characterize the study population**. In 2009, we conducted a **time-limited, prospective, multicenter (16 centers), observational study to determine the incidence, management, and short-term outcomes of newborn infants** who were intubated and mechanically ventilated at less than 72 hours postnatal age, ≥34 weeks gestation, and admitted to NRN Centers. A total of 816 infants were studied. The incidence of cardiovascular insufficiency was determined by using four different definitions as outlined in Table 2 below.

Table 2. Incidence of cardiovascular insufficiency as defined in four different ways among mechanically ventilated term and late preterm newborn infants in NRN Centers

Definition of cardiovascular insufficiency	Incidence % (n/all mechanically ventilated infants)
2 consecutive mean blood pressures < postmenstrual age in weeks	43% (351/816)
2 consecutive mean blood pressures < postmenstrual age in weeks plus sign of low systemic flow	27% (219/816)
Receipt of volume, inotropes and/or steroids	62% (503/816)
Receipt of inotropes	27% (221/816)

Reasons for initiating therapy. Sixty-two percent of these mechanically ventilated infants received treatment for cardiovascular insufficiency. The trigger for receiving therapy included low blood pressures, but low blood pressure was not the only trigger. In fact, 42% of the infants who received therapy (fluid, inotropes, or steroids) did not have cardiovascular insufficiency as defined by two consecutive mean blood pressures < postmenstrual age (PMA) in weeks. Many infants had blood pressures within normal limits for age[48] at the time therapy was initiated *(Table 3).* Of those who received fluid boluses, 60% did not have a low blood pressure as defined by a mean blood pressure less than PMA in weeks at the time of initiation of the bolus *(Table 4).* When examined for "reasons" that clinicians initiated fluid boluses, inotropes, or steroids, 42–77% received one of these therapies for low blood pressure while other reasons included poor perfusion or capillary refill >3 sec (29–49%), low urine output (9.7–14%), and metabolic acidosis (9.7–19.5%).

Table 3. Systolic, diastolic, and mean blood pressures at time of initiation of therapy. Mean (SD).

	First fluid bolus		First vasopressor dose		First steroid dose	
	<37 wks GA N = 168	≥37 wks GA N = 324	<37 wks GA N = 66	≥37 wks GA N = 149	<37 wks GA N = 30	≥37 wks GA N = 73
Systolic BP	53.3 (10.7)	58.8 (14.3)	47.9 (8.5)	52.7 (12.5)	49.2 (13.1)	55.2 (13.0)
Diastolic BP	30.5 (13.0)	43.2 (10.9)	29.5 (15.1)	31.4 (10.3)	32.2 (10.8)	36.1 (9.4)
Mean BP	38.4 (9.8)	42.4 (11.8)	35.6 (7.7)	39.1 (10.1)	39.1 (11.2)	43.4 (10.3)

Table 4. Therapy received for cardiovascular insufficiency; timing, blood pressure at time of initiation and total days of therapy. Median (25th percentile, 75th percentile); % (n/N)

	All N = 502	Volume expanders N = 488	Inotropes N = 215	Steroids N = 103
Age at 1st dose (hours)	4.0 (1.2, 15.1)	3.5 (1.1, 14.8)	12.633 (5.03, 24.7)	26.2 (12.4, 43.5)
Mean BP at 1st dose	39 (33, 47)	39 (33, 47)	36 (31, 42)	41 (35, 49)
% with mean BP <PMA	39.2% (131/334)	39.8% (137/344)	53.8% (93/173)	32.6% (30/92)
Total Days	NA	NA	2.5 (1, 5)	4 (2, 7)

The timing of therapy is outlined above in Table 4. Most infants had therapy initiated for cardiovascular insufficiency within the first 24 hours of age.

Low blood pressure was not the only clinical measure used to initiate therapy for cardiovascular insufficiency and appears to be an unreliable measure. Therefore, the presence of inotropes was used to evaluate outcomes. The patient characteristics and outcomes are listed in Tables 5 and 6. Outcomes were significantly worse in those who received inotropes vs. those who did not.

Table 5. Patient characteristics of infants who received inotropes vs. those who did not

Patient Characteristic	All Infants N=783	Inotrope N=212	No inotropes N=571	P-value
Prenatal steroid use, %	6.0 (47/778)	4.8 (10/210)	6.5 (37/568)	0.4586
Birth weight, g	3001 (646)	3145 (671)	2948 (629)	0.0001
Gestational age, wks	37.3 (2.1)	37.8 (2.1)	37.1 (2.1)	<.0001
Apgar score <3 at 5 min, %	12.1 (93/771)	18.8 (39/208)	9.6 (54/563)	0.0008
Intubation in L & D, %	39.8 (311/782)	54.7 (116/212)	34.2 (195/570)	<.0001
Cesarean section, %	55.8 (437/783)	56.1 (119/212)	55.7 (318/571)	1.0000
Male, %	60.7 (475/782)	62.7 (133/212)	60.0 (342/570)	0.5392
Outborn, %	43.6 (341/782)	30.7 (65/212)	48.4 (276/570)	<.0001
Inhaled NO, %	19.3 (151/781)	54.7 (116/212)	6.2 (35/569)	<.0001
Extra corporeal membrane oxygenation (ECMO), %	4.7 (37/781)	14.2 (30/212)	1.2 (7/569)	<.0001
Surfactant use, %	42.1 (329/781)	52.4 (111/212)	38.3 (218/569)	0.0006
Whole body cooling, %	10.8 (84/781)	22.2 (47/212)	6.5 (37/569)	<.0001

Table 6-1. Outcomes in infants who received inotropes vs. those who did not

Outcome	All Infants N=783	Inotropes N=212	No inotropes N=571	P-value
Death, %	6.8 (53/778)	15.7 (33/210)	3.5 (20/568)	<.0001
Died within 7 days, %	3.0 (23/778)	8.6 (18/210)	0.9 (5/568)	<.0001
Age at time of death	9.0 (3.0, 26.0)	7.0 (3.0, 11.0)	25.5 (8.0, 52.5)	0.0054
Days intubated and on vent	3.0 (2.0, 8.0)	8.0 (4.0, 13.0)	2.0 (2.0, 5.0)	<.0001
Days on oxygen	6.0 (2.0, 11.0)	10.0 (6.0, 17.0)	4.0 (2.0, 8.0)	<.0001
Day of life at time of full nipple feeding	9.0 (6.0, 17.0)	16.0 (10.0, 26.0)	8.0 (5.0, 14.0)	<.0001
Days in NICU	12.0 (8.0, 24.0)	16.0 (10.0, 34.0)	11.0 (8.0, 21.0)	<.0001

Table 6-2. Outcomes in infants by gestational age who received inotropes vs. those who did not; excluding infants with CDH, HIE, receipt of whole body cooling, and omphalocele,

Outcome	All Infants	Inotropes	No Hypotension by any definition	* signified p-value is <0.5 between groups
GA < 37 weeks	N = 277	N = 42	N = 115	
Death (%)	3.2	14.3	0 (0/115)	*
Died within 7 days (%)	1.4	9.5	0 (0/115)	*
Age at time of death[4]	9 (4, 16)	4 (3, 16)	NA	NA
Days intubated and on ventilator	2 (2, 5)	7 (4, 11)	2 (2, 4)	*
Days on oxygen	5 (2, 9)	10.5 (4, 16)	4 (2, 8)	*
DoL at time of full nipple feeding	9 (6, 17)	20.5 (10, 27)	8 (6, 14)	*
Days in NICU	12 (8, 24.5)	16 (10, 34)	10 (6, 17)	*

GA ≥ 37 weeks	N = 370	N = 93	N = 113	
Death (%)	4.3	9.8	2.7	*
Died within 7 days (%)	1.4	4.4	0.0	*
Age at time of death	12.5 (2, 45.5)	12 (2, 18)	48 (30, 60)	
Days intubated and on ventilator	3 (2, 8)	9.5 (4, 13)	2 (1, 4)	*
Days on oxygen	5 (2, 10)	11 (8, 18.5)	3 (1, 5)	*
DoL at time of full nipple feeding	8 (5, 15)	14 (10, 26)	6 (3, 9)	*
Days in NICU	12 (7, 21)	17 (11, 35)	8 (5, 15)	*

7. Methods/Procedures

a. Study Design

The study will be a randomized, multicenter, double-blind, placebo-controlled trial. Patients will be enrolled and randomized in a variable block design, 1:1 ratio of hydrocortisone or placebo.

b. Study Population

Inclusion criteria: Eligible infants will be ≥34 weeks gestation who are—

- Intubated and mechanically ventilated for a minimum of 2 hours before 72 hours postnatal age
- Admitted to a NRN NICU before 48 hours postnatal age.

Information will be collected on maternal and infant demographics including antenatal steroids. Data will also be collected on eligible infants who are not enrolled on the screening and eligibility form including gestational age, outborn/inborn status, and reason for not enrolling.

The exclusion criteria include those infants with cardiovascular insufficiency which is likely not due to relative adrenal insufficiency.

Exclusion criteria:

- Attending physician refusal
- No parent/guardian consent
- Infants receiving extracorporeal membrane oxygenation (ECMO)
- Infants who are intubated for the sole purpose of an anticipated surgery or airway anomalies
- Infants for whom treatment will be limited based on poor prognosis
- Receiving dexamethasone or hydrocortisone
- Receiving ibuprofen or indomethacin

Infants will be excluded if there is a known diagnosis at the time enrollment of—

- Congenital heart disease not including
  atrial septum defect, ventricular septal defect or patent ductus arteriosus
- Hypotension thought to result from specific, immediately remediable factors including placental hemorrhage, acute hemorrhage, or tension pneumothorax
- Pituitary hypoplasia or congenital adrenal hyperplasia
- Chromosomal disorder
- Hypertension in the absence of inotrope therapy as defined by a mean arterial blood pressure >95th percentile for postmenstrual age in weeks[48]
- Receipt of therapeutic hypothermia for hypoxic ischemic encephalopathy
- Severe brain structural abnormalities or periventricular leukomalacia, stroke or seizures
- Congenital diaphragmatic hernia

- Abdominal wall defects, such as gastroschisis or omphalocele
- Major renal anomalies requiring dialysis.

Infants diagnosed with pituitary hypoplasia or congenital adrenal hyperplasia will be discontinued from study drug and withdrawn from study. All other infants in whom study drug is discontinued, including those treated with ECMO after enrollment will remain in the analysis according to the intention –to- treat principle.

Timing of consent. Parents/guardians of infants who meet inclusion criteria and who do not have any of the exclusion criteria may be approached for consent for enrollment into the study, regardless of any blood pressure values or therapies planned or given for cardiovascular insufficiency**.** Infants ideally would be enrolled and randomized to study drug within 24 hours of intubation and receipt of inotropes (up to max of 96 hours of age). For transported infants, parents will be contacted for consent by telephone. Enrolling infants as soon as possible will allow more time for discussion with parents, enrollment, randomization, and receipt of study drug.

c. Study Intervention

Randomization criterion. **Decision of the clinical care team to treat with** an inotrope (dopamine, dobutamine, epinephrine, or norepinephrine) within the first 72 hours of life, at a minimum dose of 5 mcg/kg/min (epinephrine 0.01 mcg/kg/min), will be the trigger for randomization to study drug. Blood pressure will **not** be a criterion for randomization. Low dose dopamine (<5mcg/kg/min) initiated for low urine output does not qualify for randomization. Low blood pressure did not correlate with interventions for cardiovascular insufficiency in our multicenter NRN observational study *(see section 6b, Preliminary Studies, above).* However, receipt of inotrope support was associated with significantly worse outcomes, including a mortality rate of almost 16% vs. 4%. Therefore, this is a reasonable clinical indicator of adverse outcomes.

Randomization method. Randomization will be stratified by Network center using a randomly permuted block randomization algorithm devised by the NRN Data Coordinating Center at RTI. A centralized secure, password-protected web-based (Hatteras Clinical DMS) randomization process will be used to allocate infants to either hydrocortisone or placebo. The medication will be reconstituted by the pharmacist, and caregivers will remain blinded. Placebo will be normal saline and will be given in equal volume to a hydrocortisone dose and delivered at same rate.

Study Drug. Enrolled infants who receive inotrope therapy before 72 hours postnatal age **will be randomized to receive 7 days of hydrocortisone** (hydrocortisone sodium succinate, plain; will not have benzyl alcohol) given through intravenous line, po if no line or by intramuscular injection (I.M.) (if no intravenous line and infant is NPO) **or 7 days of intravenous, po or I.M. placebo** (normal saline in equal volume). Hydrocortisone dosing will be 2.5 mg/kg/day on day 1, 2 mg/kg/day on days 2 and 3, 1 mg/k/day on days 4 and 5, then 0.5 mg/kg/day on days 6 and 7.

- 1 mg/kg loading dose x 1
- 0.5 mg/kg q 6 hours x 12 doses
- 0.5 mg/kg q 12 hours x 4 doses
- 0.5 mg/kg q day x 1 dose

We will continue hydrocortisone for 7 days, weaning after the first 3 days, to avoid possible rebound hypotension and in consideration of possible down-regulation of glucocorticoid

receptors by higher cortisol concentrations.[40,49] Therapy with active drug or placebo should be instituted ideally within 12-24 hours of initiation of inotrope therapy. All other treatments will be at the discretion of the clinical care team. This real-world management design will increase generalizability of study results and improve compliance with study procedures.

Rationale for hydrocortisone dosing: see section 6, Background, for rationale on dosing.

Laboratory. One blood sample (1ml) for a cortisol level will be obtained within 4 hours prior to initiation of study drug for each enrolled patient. The sample of blood from each center will be labeled study patient ID and shipped to a central laboratory (The University of New Mexico CTSC Research Lab) in Albuquerque, New Mexico. The cortisol levels will be measured by the IMMULITE 1000 cortisol procedure (chemiluminescent system).

Blood for cortisol levels is not mandatory for study if parents wish to decline blood draw for this timed study lab. Cortisol levels obtained by clinical team will be collected from medical chart. The relationship between cortisol concentrations and response to hydrocortisone, severity of illness and outcomes will be analyzed.

The literature shows conflicting results on the value of cortisol concentrations in determining therapy. Infants often respond to glucocorticoids regardless of cortisol levels. While we found that infants with cortisol values <15 mcg/dl had positive responses to hydrocortisone in a small retrospective study,[13] other studies were unable to use cortisol values to predict the severity of illness, need for cardiovascular support, or the response to treatment.[10,14,50]

Echocardiograms. *If an echocardiogram is ordered by the clinical team, the clinical report will be labeled with patient ID and will be sent to the* NRN Data Coordinating Center at RTI*. The following measurements will be collected if available:* shortening fraction, ejection fraction presence of ductus and diameter, Left atrium to aortic ratio, presence of diastolic retrograde flow in descending aorta, velocity in left pulmonary artery, pressure gradient across PDA and shunt direction, tricuspid regurgitation, right ventricular function, evidence of pulmonary hypertension, atrial and ventricular dimensions, isovolumic relaxation and contraction times, presence of any defects and myocardial performance indices if available (some institutions do not have equipment to determine indices like wall stress).

Concurrent medications. All concurrent medications just prior and during the course of study drug administration will be recorded including dopamine, dobutamine, epinephrine, norepinephrine, milrinone, vasopressin, sedatives (i.e. morphine, fentanyl, versed), any steroids, respiratory medications (i.e. inhaled nitric oxide, surfactant), neuromuscular blockers and prostaglandins. Inotrope duration and dosing (maximum drip doses) will be specifically collected for evaluation of study drug effect in addition to collecting total fluid volume received. Inotropes and volume expanders may be given as directed by clinical team. Once patients are enrolled in the study, they will not be allowed to receive dexamethasone or indomethacin/ibuprofen while on study drug. Dexamethasone is an extremely potent glucocorticoid, and risks of using the two steroids at the same time are unknown. The concurrent use of dexamethasone for airway edema will not be allowed. The combined use of a glucocorticoid and indomethacin is associated with spontaneous intestinal perforation in very preterm newborns. Although our study population should not be at risk of this complication, it seems prudent to avoid this combination therapy. Initiation of indomethacin or ibuprofen or any anti-hypertensive medication will result in

discontinuation of study drug. Data collection will continue and all analysis will be intention to treat.

Open-label hydrocortisone will be discouraged. If the attending physician feels that it is necessary to administer open-label hydrocortisone for vasopressor (inotrope)-resistant hypotension, we will first encourage maximum vasopressor (inotrope) therapy, to include at least a dopamine dose of 10 mcg/kg/min **and** a second drug at a dose of at least 10 mcg/kg/min of dobutamine or 0.1 mcg/kg/min of epinephrine. We will recommend dosing of hydrocortisone as outlined in this protocol. The max total daily dose that any infant would receive if open-label hydrocortisone were used would be 5 mg/kg/day. Some small studies have used up to 5-7 mg/kg/day without adverse events.[15,51,52] Some providers obtain cortisol values to direct therapy but cortisol values obtained in this population have shown very little correlation to severity of illness or response to therapy we recommend, until more data is available, that cortisol values are not used to direct therapy. [10,14,51] Data collection will continue, and all analyses will be intention to treat.

d. Primary & Secondary Outcomes

Primary Outcome. The primary outcome will be death or neurodevelopmental impairment at 22-26 months. Neurodevelopmental impairment will be defined as any of the following deficits: a cognitive, language or motor score less than 1 SD below the mean on the Bayley Scales of Infant Development III (BSID), gross motor functional (GMF) level ≥1, visual impairment or blindness in any eye, hearing impairment, or seizure disorder. The disability can be mild, moderate, or severe and will be defined as per the NRN standard definitions at the time of assessment (general definitions are listed in Table 7). Assessment will be performed by certified NRN examiners who will be blinded to treatment assignment group. From previous NRN trials, we anticipate a follow-up rate of 90%. At the time of follow-up, a medical history will be obtained; growth parameters and a BSID-III neurological and vision examination will be performed.

Table 7. Disability definitions

Disability Severity	Exam Component	Criteria
Mild-to-moderate	Bayley Scales (a)	BSID cognitive score >1 SD below mean but not >2 SD BSID language score >1 SD below mean but not >2 SD BSID motor score >1 SD below mean but not >2 SD
	NF05 Impairment (b)	GMF level of 1 or 2 Any seizure disorder[1] Any hearing deficit [2]
	Other impairment (c)	Visual impairment [3]
Severe	Bayley Scales (A)	BSID cognitive score >2 SD below mean BSID language score >2 SD below mean BSID motor score >2 SD below mean
	NF05 Impairment (B)	GMF level 3 or greater Blindness[4] Profound hearing loss[5]

1. Any active or history of seizure(s) or seizure disorder, as noted in history or by chart review.
2. Hearing deficit where there is some amplification required (hearing aids or cochlear implants) in one or both ears as noted by history or chart review that does not reach level of profound hearing loss as defined in the severe category.

3. Visual impairment in one or both eyes per NRN standard follow-up (wears or was prescribed corrective lenses or other abnormality or blind but some functional vision) from chart review or history that does not reach level of blindness as defined in the severe category.
4. Blindness (no useful vision) per NRN standard follow-up as noted by history or chart review.
5. Profound hearing loss per NRN standard follow-up (in any ear as noted by inability to understand commands or communicate with examiner with or without amplification) by history or chart review.

Level of Disability	Definition
Normal	None of either (a) or (b) or (c)
Mild	Any of (a) but none of (b) or (c), OR Any of (b) or (c) but none of (a)
Moderate	At least one from each of (a) and [(b) or (c)]
Severe	At least one of (A) or (B)

Secondary Outcomes. Secondary outcomes will include measures of severity of illness using the oxygenation index and respiratory severity score (mean airway pressure X Fio2), [53] cardiovascular stability (Table 8) and short-term outcomes prior to discharge *(*Table 9). Measures of short term outcomes and cardiovascular stability will be compared between groups and in relation to each other.

Table 8. Cardiovascular measures

Blood Pressure	Blood pressure from before to after study drug administration (continuous)
Heart Rate	Heart rate from before to after study drug administration (continuous)
Fluid (volume) Administration	Presence and number of fluid boluses given prior to study drug and during the study drug administration.
Inotrope Administration	The presence of inotrope initiation & presence of inotrope exposure at days of life 3, 5 & 7 (dichotomous)
Inotrope Duration	Number of total days (complete 24 hours=1 day) an infant remains on any inotrope (continuous)
Inotrope Total Dose	Peak dose in 24-hour periods for 10 days after initiation of study drug.

Table 9. Short-term outcomes

Duration of mechanical ventilation	Number of days of laryngeal intubation and mechanical ventilation
Days to full feeds	Day of age when enteral feeds ≥ 120 cc/kg/day (continuous)
Need for gastrostomy tube	Need for gastrostomy tube before discharge (dichotomous)
Duration of O_2 requirement	Number of days on oxygen while in hospital (continuous)
Need for home oxygen	Infant was discharged to home on oxygen (dichotomous)
Length of hospital stay	Number of days from birth to date of first discharge (continuous)
Renal insufficiency	Presence of creatinine >2.0 in first 7 days of age (dichotomous)
NEC	Presence of NEC stage II or greater at any time prior to discharge (dichotomous)
Death	Presence of death before discharge (dichotomous)
Head imaging	Any result from head imaging performed by the clinical care team (head ultrasound, magnetic resonance imaging, CT scan); no abnormalities noted, IVH, PVL
ECMO therapy	ECMO administered at any time while in hospital

e. *Sample* Size Estimate

Determining a sample size based on available data is limited by the available studies on long-term outcomes including neurodevelopmental impairments or death in term and late preterm infants who have cardiovascular instability and require cardiovascular support. This sample size is based on the best available data, which is closest to the population proposed to study. Based on previous data, the incidence of death or any neurodevelopmental impairment (permanent hearing loss, blindness, moderate or severe cerebral palsy or Bayley MDI or PDI scores <70) was 32% in a similar population of critically ill newborn infants with respiratory distress and in need of mechanical ventilation, but excluding congenital diaphragmatic hernia defects.[39] Based on 4 additional studies in similar populations of term and late preterm infants with respiratory failure, the average incidence of death or any neurodevelopmental impairment was 30%.[54,55,56,57] If these studies had all included mild impairment the event rate would have been higher.

The trial is powered at 80% to detect a reduction in the primary outcome of death or any neurodevelopment impairment at 22-26 months from 30% to 20%, for a relative risk reduction of 33%, and a relative risk of 0.67, using a two tailed test with 5% Type I error. Allowing for 10% attrition, the required sample size for this scenario is 646 (Table 10). This sample size will also provide >80% power to detect treatment differences in important secondary outcomes of days in the NICU, intubated and on a ventilator and hours on inotropes without adjusting for multiple comparisons (Table 11)."

Table 10. Enrollment/time/consent estimates

Reduction in death or neurodevelopment delay at 22-26 mo	Total enrollment (including 10%loss)	Months to complete enrollment if consent rate 60%	Months to complete enrollment if consent rate 70%
10%	646	48	41

Because of the lack of data on outcomes in this population with which to ascertain power calculations with high confidence, the overall event rate of any NDI or death in this population will be calculated either: 1 year after the first patient is evaluated at 22-26 month follow-up or after 30% of a planned enrollment of 646; whichever occurs first. At this point, the number needed to achieve 80% power, to detect a difference of 10% with an alpha of 0.05 and a 2 sided t-tail test, will be recalculated.

Table 11. Secondary outcome effect sizes

	Our previous baseline data	Effect size	Sample size per group
Days in NICU	17.3	3 days	310
Days on ventilator	8.4	2 days	140
Hours on inotropes	81.4	24 hours	179

f. Analytical Plan

All analysis will be conducted by intention-to-treat analysis. To ensure that randomization has achieved the desired balance, all demographics will be compared

using Fisher's exact or chi-square tests for categorical factors and t tests or non-parametric tests for continuous outcomes. Dichotomous outcomes including the primary outcome will be compared between the hydrocortisone-treated group and control groups while adjusting for NRN center differences using robust Poisson regression, so that adjusted relative risk estimates of the treatment effect can be obtained. For continuous outcomes, non-normally distributed data may be log-transformed prior to analysis. Secondary analyses may be performed adjusting for gestational age or other critical baseline covariates that may be imbalanced across the two treatment groups, in addition to center. Short-term continuous outcomes will be compared between those receiving hydrocortisone and those on placebo using linear regression adjusting for NRN center and other critical baseline covariates that may be imbalanced.

g. Available Population

With all NRN Centers enrolling into the observational study (which also excluded those with major congenital heart disease, acute hypotension resulting directly from known acute maternal and/or fetal hemorrhage within 24 hours prior to delivery, pituitary hypoplasia, congenital adrenal hyperplasia, or known chromosomal disorder), ~100-115 mechanically ventilated infants in this gestational age range are admitted to NRN Centers each month and 25% of these received inotropes (21% if exclude encephalopathy, CDH, and omphalocele and those who receive cooling for HIE). We, therefore, anticipate ~22 to 25 eligible infants each month.

Infants in the same age group within the NRN with hypoxic ischemic encephalopathy may be eligible for the ongoing cooling studies in the NRN. However, infants who are cooled or have HIE will be ineligible for this study.

h. Estimated Recruitment Time

With 60% consent, 48 months would be needed to enrollment goal. Anticipating delays in startup and missed infants, study enrollment should be completed in a little over four years.

8. Risks and Benefits

Short-term adverse events. The following will be reported within 72 hours of diagnosis and 24 hours of discovery:

- *Mortality*. No study of hydrocortisone therapy in newborns or in other critically ill populations has shown an increase risk in mortality, and some have shown decreased risk of death.[11,12] This study population is at high risk of death from the underlying diseases (1.2%–11%).[18,39]
- *Late-onset (≥ 5 days) culture-confirmed infection*. Recent large randomized controlled trials in adults and preterm newborn infants showed no increased risk of infection from 7–14 days of glucocorticoid treatment.[2,5] However, culture-proven late onset infection will be tracked and reported. Early and late onset culture-proven infection in this population is 1.4% and 4.2% respectively (Vermont Oxford Network 2009). Anticipated incidence <4.2%.
- *Gastrointestinal perforation*. In contrast to the extremely low birth weight infant where the incidence of spontaneous intestinal perforation is 4%, this patient population is

developmentally more mature and should not be at risk for this event, particularly since these patients will not be simultaneously exposed to indomethacin.[14]

- *Hypertension.* These infants are often on inotropes, which often cause high blood pressure by themselves. Glucocorticoids' actions are to increase blood pressure. It is unknown if the combination of these two therapies results in a higher occurrence of hypertension. This will be tracked by counting the number of 12-hour periods in which the blood pressure was higher than 95thpercentile for weight and age and the receipt of any antihypertensive medication.[48] Incidence is unknown.
- *Hyperglycemia.* Higher dose glucocorticoids can raise blood glucose levels acutely and for short periods of time (hours), without long-term consequences. No study to date has shown a need for insulin secondary to glucocorticoid administration for the treatment of hypotension. Data on the use of insulin will be collected if administered during the study drug time and when glucose is >180mg/dl on at least two determinations at least 6 hours apart.[14] Anticipated incidence <1%.

Other Potential issues

- *Adrenal suppression*. Even in the most premature infants, this brief period of therapy has not previously been associated with adrenal suppression.[58] If any infant shows signs consistent with adrenal insufficiency after discontinuation of the study drug (hypotension, oliguria, hyponatremia, hyperkalemia), a blood sample can be sent for cortisol and therapy with hydrocortisone reinstituted if deemed necessary by the clinical care team.
- *Neurodevelopmental deficits*. The neurodevelopmental benefits or risks of using hydrocortisone for the treatment of cardiovascular insufficiency is unknown. This RCT will be an important addition to the literature regarding long-term risks/benefits of this therapy.[59] No previous study has shown adverse neurodevelopmental effects of hydrocortisone treatment in the newborn period in extremely low birth weight infants.[52,60,61] Because this study population is more mature, it is even less likely to adversely impact this proposed study population; however, our study design will enable us to evaluate that issue.
- *Persistent hypotension*. Infants will be treated in the routine manner by the attending clinicians in their respective centers to allow real-world design. Open-label hydrocortisone is discouraged but if given, the recommended plan is listed in the methods section above. Data on infants who receive open-label hydrocortisone will be collected and/or on infants who receive 3 different types of inotropes or more.

Data Safety and Monitoring Committee (DSMC) Safety Monitoring.

a. Adverse events to be monitored

Adverse events to be monitored will be those previously associated with glucocorticoid therapy, including hyperglycemia, hypertension and gastrointestinal perforation. Any infant who develops new, sustained hyperglycemia (>180mg/dl on at least two determinations at least 6 hours apart or receiving insulin) or new, sustained hypertension (mean arterial pressure >95th percentile for age on four serial determinations over at least 12 hours or receiving antihypertensive) may have study drug held or discontinued if, in the opinion of the attending neonatologist, there is no plausible alternative explanation for these findings (such as new thrombus). Not enrolling very preterm infants and excluding infants receiving indomethacin/ibuprofen should minimize the possibility for spontaneous GI perforation. These short term adverse events as defined here, should be reported within 24 hours of discovery to PI.

Also similar to the NRN hydrocortisone extubation trial, we will also specifically monitor for signs of adrenal insufficiency for 3 days after study drug is discontinued, including hypotension and oliguria, as well as hyponatremia and hyperkalemia on clinically obtained electrolyte specimens. Signs of adrenal insufficiency within 3 days after study will be reported within 24 hours of discovery. Previous studies of hydrocortisone at various doses have not reported these signs after discontinuation of a tapering course of the drug.

Patients who develop hypotension and oliguria (shock) significant enough in the judgment of the attending neonatologist to require support with volume and/or vasopressors may have a clinically indicated blood sample drawn for cortisol and may be restarted on hydrocortisone or other therapy for shock at the discretion of the clinical attending. Open-label hydrocortisone should be given at a test dose of 1mg/kg, with continuation of the therapy based on clinical response to the first dose. Persistent hypotension despite inotrope therapy and study drug will be treated per the routine of each center as directed by the treating clinician. Open-label hydrocortisone use will be considered a protocol deviation and it will be reported to DSMC if this deviation occurs in more than 20% of those enrolled.

Serious adverse events to be reported to NICHD within 24 hours include death, late onset sepsis, hyperglycemia receiving insulin, hypertension receiving antihypertensive medication or intestinal perforation with an assessment as best as possible as to the cause of the perforation (NEC, spontaneous, other).

b. Interim safety monitoring

The DSMC will compare the incidence of death and a composite of serious adverse events including death, late onset sepsis, intestinal perforation, and hyperglycemia requiring insulin between the two treatment arms after every 100th infant reaches status (death, discharge, transfer or 60 days of age). Since 646 infants are to be enrolled in this trial, this will involve interim looks approximately once every 9 months, or after the enrollment of every additional 160 infants, giving a Pocock boundary of 2.413, with a corresponding significance level of $p<0.0158$ (Pocock, 1977). Such reports will be forwarded to the Chair of the DSMC when there is any suggestion of a trend towards a difference between the two treatment arms emerging. They will also be made available to the full DSMC at their scheduled meetings after 50% and 75% of the trial infants reach status as defined by the GDB. Interim efficacy analysis using O'Brien-Fleming stopping bounds will also be made available to DSMC when 50% of primary outcome data is available.

Nomenclature

ACTH	adrenocorticotropic hormone
ARDS	acute respiratory distress syndrome
BP	blood pressure
BSID	Bayley Scales of Infant Development
CLD	chronic lung disease
CRH	corticotrophin-releasing hormone
CT	computed axial tomography
DSMC	Data Safety and Monitoring Committee
ECMO	extracorporeal membrane oxygenation
GA	gestational age
GMF	gross motor function
HPA	hypothalamic-pituitary-adrenal
HUS	head ultrasound
IVH	intraventricular hemorrhage
NEC	necrotizing entercolitis
NICU	newborn intensive care unit
NRN	Neonatal Research Network
PMA	postmenstrual age
PVL	periventricular leukomalacia
RCT	randomized controlled trial
SD	standard deviation
SIP	spontaneous intestinal perforation

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