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## Barriers to enrollment in a randomized controlled trial of hydrocortisone for cardiovascular insufficiency in term and late preterm newborn infants

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### Conflict of interest:

No authors report conflicts of interest for this study

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## Abstract

**Objective**—To analyze reasons for low enrollment in an RCT of the effect of hydrocortisone for cardiovascular insufficiency on survival without neurodevelopmental impairment (NDI) in term/late-preterm newborns.

**Study Design**—The original study was a multicenter RCT. Eligibility: 34 weeks' gestation, <72° old, mechanically ventilated, receiving inotrope. Primary outcome was NDI at 2 years; infants with diagnoses at high risk for NDI were excluded. This paper presents an analysis of reasons for low patient enrollment.

**Result**—257 of 932 otherwise eligible infants received inotropes; however, 207(81%) had exclusionary diagnoses. Only 12 infants were randomized over 10 months; therefore, the study was terminated. Contributing factors included few eligible infants after exclusions, open-label steroid therapy, and a narrow enrollment window.

**Conclusion**—Despite an observational study to estimate the population, very few infants were enrolled. Successful RCTs of emergent therapy may require fewer exclusions, a short-term primary outcome, waiver of consent, and/or other alternatives.

**Clinical trial registration**—[Clinicaltrials.gov, NCT01954056](https://clinicaltrials.gov/ct2/show/study/NCT01954056)

## Introduction

Cardiovascular insufficiency, defined as inadequate blood flow to meet metabolic needs, frequently complicates hypoxic respiratory failure in critically ill term and late preterm newborns admitted to newborn intensive care units (NICUs)<sup>1</sup>. Critically ill term and late

preterm infants presenting with low blood pressure, prolonged capillary filling time, low urine output, and/or metabolic acidosis, frequently receive fluid boluses, inotropic drugs, and, with increasing frequency, hydrocortisone to improve systemic blood flow<sup>1,2</sup>. One large observational study reported that 21% of all mechanically ventilated infants born at 34 weeks gestation were treated with an inotrope, and 41% of those treated with an inotrope were also treated with hydrocortisone<sup>2</sup>. Although some of these therapies have been tested in extremely preterm infants, no randomized controlled trials (RCTs) have tested the effects of any of these therapies on short or long-term outcomes in the critically ill term and late preterm population. Small studies in these infants have reported that many infants with cardiovascular dysfunction have low cortisol concentrations<sup>3-7</sup>. Case series and retrospective studies have also demonstrated improved cardiovascular stability following hydrocortisone treatment<sup>7-9</sup>; however, no RCT has evaluated the effects of hydrocortisone on cardiovascular function, short-term in-hospital outcomes, or long-term neurodevelopment in term and late preterm infants.

To design a randomized trial of hydrocortisone for cardiovascular insufficiency in this population, we first performed an observational study to document: (1) the relationship of blood pressure to the receipt of treatment for cardiovascular insufficiency; (2) the utility of four specific definitions of cardiovascular insufficiency to predict short-term outcomes; and (3) the availability of sufficient numbers of infants for the planned study.<sup>1,2</sup> We found little correlation between blood pressure values and treatments administered; however, infants receiving inotropic therapy had significantly higher incidence of many short-term adverse outcomes, including mortality<sup>1,2</sup>. Therefore, we chose receipt of inotropic therapy as a reasonable and clear criterion for study entry, and undertook a multicenter RCT to determine the short- and long-term effects of hydrocortisone treatment for cardiovascular insufficiency in critically ill term and late preterm infants in the Eunice Kennedy Shriver National Institute for Child Health and Human Development (NICHD) Neonatal Research Network (NRN). Because death or neurodevelopmental impairment (NDI) at 2 years was considered a much more important outcome than a short-term measure (e.g., length of inotropic therapy), we chose this as the primary study outcome.

During the study enrollment period (August 2014 – July 2015), all infants admitted to participating centers were screened for eligibility. Of 932 who met initial eligibility criteria (Figure: 34 weeks of gestation, intubated and mechanically ventilated), 257 (28%) received inotropic support. However, 207 (81%) were excluded for one or more of the pre-specified criteria (Table 1), and only 12 infants were enrolled. For that reason, the NRN Steering Committee voted to terminate the study on July 28, 2015, due to the inability to enroll the planned sample size in a reasonable period. This paper presents the results of our analysis of barriers to enrollment in the RCT.

## Methods

### (1) RCT study design

The original study was a randomized, multicenter, double-masked, placebo-controlled trial conducted at 16 centers of the Eunice Kennedy Shriver National Institute of Child Health and Human Development's Neonatal Research Network (NRN) centers. Institutional review

boards at all study sites approved the study and eligible patients were enrolled after parental consent. All infants admitted to the newborn intensive care unit(s) at the study sites were screened for eligibility. Infants were eligible if they were  $\geq 34$  weeks' gestation, admitted to a study site before 48 hours' postnatal age, intubated and mechanically ventilated for at least 2 hours in the first 72 postnatal hours, and met the study definition of cardiovascular insufficiency: receipt of dopamine or dobutamine at  $\geq 5$  mcg/kg/minute or epinephrine or norepinephrine at  $\geq 0.01$  mcg/kg/min. The primary study outcome was death or neurodevelopmental impairment (NDI) at 22 – 26 months. Exclusions to study are shown in Table 1, and included diagnoses that placed infants at high risk of neurodevelopmental impairment, as well as open-label glucocorticoid treatment. Randomization was stratified by Network center using a randomly permuted block algorithm through a centralized web-based process. A sample size of 646 infants was chosen to detect a difference of 10 percentage points in the primary outcome, with 80% power.

## Procedures

Based on limited pharmacokinetic and clinical effect data<sup>10</sup>, hydrocortisone was given as a 1 mg/kg loading dose followed by 0.5 mg/kg q 6 hours x 12 doses, 0.5 mg/kg q 12 hours x 4 doses and 0.5 mg/kg q day x 1 dose, for a total treatment course of 7 days. Placebo was an equal volume of normal saline. One blood sample (1 ml) was obtained for cortisol assay 4 hours before starting study drug from each enrolled patient whose parent gave consent. All samples were analyzed by one laboratory (University of New Mexico Clinical and Translational Science Center Core Laboratory). Indomethacin and ibuprofen were not permitted during the study drug treatment period because of the potential interaction of non-steroidal anti-inflammatory agents with glucocorticoids<sup>11</sup>.

## (2) Analysis of barriers to study entry

As study enrollment proceeded and far fewer infants were enrolled than anticipated, detailed delineations of reasons for non-enrollment were acquired from each center and evaluated. These reasons appeared to stem primarily from factors that could not be changed within the study protocol; therefore, patient enrollment was terminated. This report presents the results of the investigation into the reasons for lack of enrollment.

## Results

The first centers began screening in August of 2014 and by July 2015, all 16 study centers were screening. At that time, seven sites had been screening for  $>6$  months. During the patient screening period, 932 infants were admitted to the study centers and met the screening entry criteria of being  $\geq 34$  weeks of gestation, intubated and mechanically ventilated, and admitted to an enrolling NRN center at  $<48$  hours postnatal age (Figure). Of these, 257 (28%) infants were receiving  $\geq 5$  mcg/kg/minute of dopamine or equivalent inotrope dose, similar to the percentage in the observational study<sup>2</sup>. Of these infants, however, 207 (81%) were excluded for one or more of the pre-specified criteria (Table 1, Figure), leaving 50 infants eligible. The parents of 21 of these infants were approached for consent, and 12 (57%) consented to the study. Reasons that 29 families were not approached for consent are detailed in the Figure. In view of continuing low enrollment (3 infants in the

final 3 months), enrollment was suspended on July 23, 2015. The NRN Steering Committee voted to terminate the study on July 28, 2015, due to the inability to enroll the planned sample size in a reasonable period.

Of the 12 enrolled infants, four were late preterm and eight were term. Median age at study enrollment was 37 hours, with a range of 2 to 46 hours. Primary diagnoses for the 12 enrolled patients are shown in Table 2, and are compared with the distribution of those diagnoses in the previous observational study. Eight infants (67%) had blood drawn for pre-treatment cortisol concentration, and values were 10.8 [6.1 – 16.3], 2.0 – 222 mcg/dL (median [25 – 75%ile], range).

## Discussion

Critically ill term and late preterm infants are frequently exposed to therapies intended to treat cardiovascular insufficiency, including fluid boluses, inotropes and, increasingly, hydrocortisone<sup>1,2</sup>. Unfortunately, none of these therapies has been subjected to a large randomized controlled trial of short- and long-term outcomes in the term and late preterm population. The objective of this RCT was to evaluate the efficacy and safety of hydrocortisone treatment for cardiovascular insufficiency in a large, multicenter RCT of critically ill, mechanically ventilated term and late preterm infants; however, we failed to achieve that objective due to low patient enrollment. We therefore sought to characterize the reasons for low enrollment in this study, to aid in planning future studies in critically ill newborn infants.

We found three specific factors to be important contributors to low enrollment. First, although a reasonable number of potentially eligible patients were admitted, the choice of neurodevelopmental impairment (NDI) as the primary outcome measure, and the accompanying exclusion of infants at high risk for NDI, resulted in the loss of the majority of otherwise eligible patients (193 of 257, Table 1). The most frequent diagnoses resulting in exclusion for this reason were hypoxic-ischemic encephalopathy (HIE), congenital anomaly, congenital heart disease, and CNS or chromosomal abnormality. Death or NDI was chosen as the primary outcome because it was thought to be much more significant than a short-term benefit such as decreased time on inotropic support<sup>12</sup>. Unfortunately, the choice to exclude groups of infants at high risk for abnormal neurodevelopmental outcomes was the major contributor to the failure of the study. We can speculate that if these patients had been included in the study and balanced in the randomization, valuable information about the efficacy of hydrocortisone therapy in these high-risk groups would have resulted. However, it is also possible that the variable effects of the different diagnoses or an unbalanced randomization would have hopelessly confounded the interpretation of the study results. From our results, it would appear that designation of a short-term measure as the primary outcome, including groups at high risk for neurodevelopmental difficulties, would be the only way to achieve adequate patient enrollment. Neurodevelopmental outcomes at age two would then be a secondary outcome.

The second major barrier to enrollment was the use of open-label glucocorticoid prior to study entry in 72 (28%) of the infants. While 39 of these infants had an additional reason for

exclusion, steroids alone were the reason for exclusion of 33 infants, 13% of the potentially eligible population. In the observational study, the median time of the first glucocorticoid dose was 25 hours for term and 33 hours for late preterm infants, and it was hoped that these infants could be enrolled in the RCT before steroids had been administered. However, the median age at randomization into the RCT was 37 hours, and 72 infants had received open-label glucocorticoid treatment prior to randomization. Only 4 patients were excluded due to physician refusal, suggesting that lack of physician equipoise was not a major issue; however, the number of infants receiving glucocorticoids before the median enrollment age of 37 hours suggests a clinical bias in favor of hydrocortisone treatment. Faced with a critically ill patient with evidence of cardiovascular insufficiency, clinicians may reasonably feel an urgency to treat quickly, with multiple therapeutic agents if necessary, to raise the blood pressure and improve the circulation. This leaves the research team with a very narrow window for approaching the family for consent and obtaining the study drug from the investigational pharmacy. In some cases, families were not approached for consent for this reason.

The third major barrier to enrollment was difficulty in obtaining consent and randomizing infants in the narrow enrollment window, leading to a lower than expected enrollment rate (24%). The consent rate for families who were approached for consent was similar to other interventional studies of medications in common use in the NICU, at 57% (12 of 21)<sup>13</sup>. However, consent was not requested in 29 other cases. Some parents were not available; however, for many others, despite 24/7 screening, the process of participant identification, parental consent, and randomization proved too time-consuming to enable patients to be enrolled in the study prior to open-label glucocorticoid therapy. Alternative approaches to obtaining consent, such as approaching parents when their infants are first admitted and preparing study drug at that time, might increase enrollment. However, as only 28% of the initially eligible population ever received inotropic support, this method would greatly increase the amount of time and resources required for each patient enrolled.

In addition to specific barriers to enrollment in this study, we also noted a decline in the number of eligible infants. Based on the observational study, we anticipated an eligible population of >125/year, even after allowing for the specified exclusions. The decreased number of eligible infants we encountered between 2009 and 2015 is consistent with clinical perceptions and with other studies documenting that fewer term and late preterm infants are being intubated and mechanically ventilated in recent years<sup>14–17</sup>.

In summary, enrollment in this study was handicapped by a number of factors. First, the choice of long-term neurodevelopment rather than short-term cardiovascular effects as the primary study outcome resulted in the exclusion of the preponderance of otherwise eligible patients. Second, the process of obtaining informed consent from overwhelmed families just after the birth of an unexpectedly critically ill infant is delicate, difficult, and time consuming, resulting in a detrimental delay in study entry, with exclusion of additional infants due to intervening glucocorticoid exposure. The combination of these challenging factors made the timely and successful completion of this study impossible. Although determining the effect of therapies for cardiovascular insufficiency on survival without neurodevelopmental impairment may well be more important than short-term effects, this

was not feasible as a primary outcome in our study. In retrospect, it may have been more practical to choose a short-term primary outcome (e.g., days on inotropic therapy), with long-term neurodevelopment as a secondary outcome, resulting in a much larger population of eligible infants. In addition, as others have noted, fewer term and late preterm infants are presenting over time with diagnoses such as those in Table 2.

Critically ill term and late preterm infants remain a population at high risk for clinically important adverse outcomes as well as for adverse consequences from the use of off-label, unproven therapies. None of the therapies commonly used to treat cardiovascular insufficiency in term or late-preterm newborn infants has been subjected to a rigorous randomized controlled trial that includes monitoring of long-term outcomes, yet most such infants are exposed to one or more of these therapies<sup>1,2</sup>. Barriers to successfully performing rigorous clinical studies foster the adoption of unproven therapies, which in turn make such studies more difficult to perform. Alterations in study design, such as (1) accepting short-term effects on cardiovascular function as a primary outcome in order to include more patients; (2) obtaining a waiver of consent from institutional review boards to enable more expeditious enrollment and drug initiation for therapies in common use in the NICU; (3) utilizing the clinical pharmacy to prepare study drugs that are in current use for more timely delivery to the bedside; or other alternatives, will be necessary to achieve the vital goal of understanding the effects of therapeutic interventions in this critically ill population.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Abbreviations and acronyms

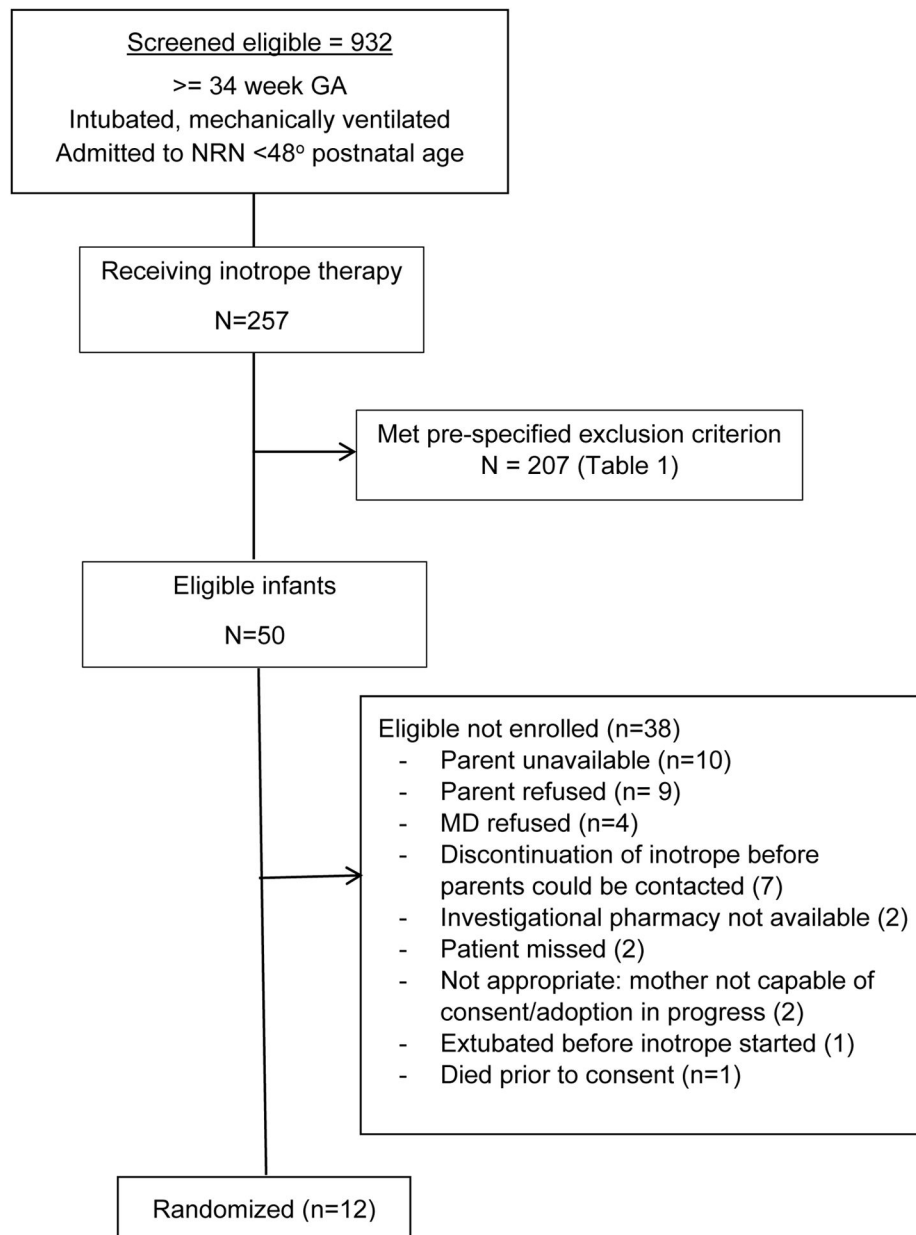
<b>RCT</b>	Randomized controlled trial
<b>NDI</b>	Neurodevelopmental impairment
<b>NRN</b>	Neonatal Research Network, Eunice Kennedy Shriver National Institute of Child Health and Human Development
<b>BSID-III</b>	Bayley Scales of Infant Development III
<b>GMCFS</b>	Gross Motor Function Classification System
<b>iNO</b>	inhaled nitric oxide

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**Figure 1.**  
Consort flow diagram

**Table 1**

Infants excluded from the RCT

Met exclusion criterion <sup>a</sup> Total excluded: 882 of 932	Percentage of all screened infants (N=932) N (%)	Of infants on inotrope therapy meeting study entry criteria (N=257) N (%)
Major anomaly (including diaphragmatic hernia)	228 (24.5%)	75 (29.2%)
Prior dexamethasone or hydrocortisone	79 (8.5%)	72 (28%) <sup>b</sup>
Therapeutic hypothermia for HIE	146 (15.7%)	58 (22.6%)
Congenital heart disease	108 (11.6%)	35 (13.6%)
ECMO	28 (3.0%)	22 (8.6%)
Structural CNS abnormality	30 (3.2%)	14 (5.4%)
Limited treatment for poor prognosis	29 (3.1%)	13 (5.1%)
Chromosomal disorder	37 (4.0%)	11 (4.3%)
Intubated for surgery or airway anomaly	73 (7.8%)	5 (1.9%)
Ibuprofen or indomethacin <24hrs prior	2 (0.2%)	1 (0.4%)
Hypotension due to treatable cause (e.g., hemorrhage or pneumothorax)	6 (0.6%)	3 (1.2%)
Hypertension > 95th percentile	9 (1.0%)	1 (0.4%)
Pituitary hypoplasia or congenital adrenal hyperplasia	1 (0.1%)	0 (0.0%)

<sup>a</sup>An infant may have met more than one exclusion criterion<sup>b</sup>Only 33 of these were excluded for the sole reason of prior dexamethasone or hydrocortisone therapy.

**Table 2**Comparison of primary clinical diagnoses in the observational study and the RCT<sup>a</sup>

	Observational study	RCT
Respiratory distress syndrome	68%	8 (75%)
Pneumothorax/mediastinum	15%	2 (17%)
Meconium aspiration syndrome	14%	7 (58%)
Pneumonia	10%	1 (8%)
Necrotizing enterocolitis	0	1 (8%)
Persistent pulmonary hypertension	19%	5 (42%) <sup>b</sup>

<sup>a</sup>An infant may have multiple diagnoses<sup>b</sup>All infants with persistent pulmonary hypertension also had one or more of the other diagnoses in the Table

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