Randomized Controlled Trial of Home Therapy with Caffeine Citrate in Moderately Preterm Infants with Apnea of Prematurity

Short Title: Moderately Preterm Infants with Caffeine at Home for Apnea (MoCHA) Trial

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SECTION 1. ABSTRACT

Objective

To evaluate the effect of continuing treatment with caffeine citrate in the hospital and at home in moderately preterm infants with resolved apnea of prematurity on days of hospitalization after randomization.

Study Design

Randomized, 1:1 allocation with parallel enrollment, double-blinded, placebo-controlled, multicenter trial.

Primary Outcome

The primary outcome of the study will be the number of days of hospitalization from randomization to discharge up to 48 weeks post-menstrual age (PMA), with censoring at time of transfer or death.

Secondary Outcomes

The secondary outcomes of the study will be:

a. The number of days to physiologic maturity after randomization up to 48 wks PMA.

   Physiologic maturity will be defined as follows:
   i. Temperature: out of the incubator for at least 48 hours with normal body temperature
   ii. Feeding: oral feeding at a volume of at least 140 ml/kg/day or growing on less than 140 ml/kg/day for at least 48 hours
   iii. Respiratory: apnea-free for at least 5 consecutive days

b. Post menstrual age at discharge up to 48 wks PMA, censoring at time of transfer or death (status).
c. The number of all cause readmissions, including apneic events and apparent life-threatening events (ALTE), to the hospital within the first four weeks, second four weeks, and first eight weeks combined after discharge from the hospital by 48 wks PMA.
d. The number of all cause sick visits to urgent care, emergency room or health care provider office within the first four weeks, second four weeks, and first eight weeks combined after discharge from the hospital by 48 wks PMA.
e. Safety outcome measures pre-hospital discharge
   - Weight gain from randomization until status (discharge up to 48 wks PMA, with censoring at time of transfer or death). The weight gain may also be assessed using percentiles including birthweight percentiles.
   - The number of days after randomization until status that infant had at least two consecutive heart rates >200 documented at least 3 hours apart (when infant not crying).

- Treatment for high blood pressure initiated after randomization until status.
- The number of episodes between randomization and status that infant was placed NPO for ≥ 24 hours.
- The use of anti-reflux medications started between randomization and status
- The number of days that significant apnea/bradycardia, as defined by documentation of infant receiving any of the following between randomization and status: open label caffeine, other methylxanthines, doxapram, CPAP or ventilatory support for apnea/bradycardia.
- The presence of documented and treated arrhythmias between randomization and status, not due to tachycardia or bradycardia.
- The onset of documented seizures, as defined by treating with anti-convulsants, between randomization and status.

f. Death

Evaluation of infants during the first four weeks, second four weeks, and first eight weeks combined after discharge from the hospital is done to determine whether there is a difference in post-discharge secondary outcomes on caffeine (first four weeks), off caffeine (second four weeks), and in overall outcomes after discharge home (first eight weeks).

A short discussion on the hypothetical cost-savings by the reduction in number of days of hospitalization as a financial benefit of the trial's intervention (caffeine versus placebo) will be added to the discussion section of the manuscript at the conclusion of the trial.

Eligibility Criteria

Inclusion Criteria

Inborn and outborn infants of 29 $^{0/7}$ to 33 $^{6/7}$ weeks gestational age at birth admitted to hospitals of the National Institute of Child Health and Human Development Neonatal Research Network (NRN) ≤ 72 hours of age and who at time of enrollment are:

a. 33 $^{0/7}$ - 35 $^{6/7}$ weeks post-menstrual age at the time of randomization
b. Receiving caffeine with plan to discontinue treatment or just discontinued caffeine treatment
c. Receiving feeds at a volume of ≥120 ml/kg/day by oral and/or tube feeding
d. Ability to start study medication within 72 hours after stopping caffeine

Exclusion Criteria

a. On respiratory therapy (oxygen more than room air equivalent for high altitude sites, nasal cannula, continuous positive pressure ventilation, and/or mechanical ventilation).
b. Infants who would otherwise be discharged home on apnea monitor due to underlying disease or family history, including history of a sibling with sudden infant death syndrome
c. Parental request for apnea monitor
d. Congenital heart disease other than atrial septal defect, ventricular septal defect, or patent ductus arteriosus

e. Neuromuscular conditions affecting respiration
f. Major congenital malformation and/or genetic disorder
g. Plans to transfer to a non-NRN site before discharge
h. Unable to obtain parental or guardian consent

Study Intervention/Methods

Study subjects will be patients in the NICU at one of the participating hospitals at a Neonatal Research Network site. Infants who meet the eligibility criteria will be randomized to either caffeine citrate at 10 mg/kg/dose (5 mg/kg caffeine base) or a placebo (equal volume of all the excipients except for the active ingredient, caffeine citrate) to be given daily, not less than 12 hours between doses, beginning within 72 hours of open label caffeine discontinuation. The infant may still require hospitalization for observation after discontinuation of open label caffeine or for other discharge issues such as temperature control or feeding tolerance.

Infants who will continue caffeine citrate or placebo at home for the first 28 days after hospital discharge, will have a weight obtained within 48 hours of discharge to be used for dosage calculation. On the day of discharge, the parent will be supplied with 28 numbered vials with oral caffeine citrate (intervention group) or placebo at an equivalent volume (placebo group). Oral syringes will be provided to the parents to draw up doses. The parents will be educated by the research nurse, discharge nurse, physician, or pharmacist on storage and administration of study medication. A member of the research team will contact the parents to obtain post-discharge information within 72 hours after discharge, once a week for the first 4 weeks, and biweekly during the weeks 5 to 8 after discharge.

Sample Size

To obtain a two-day difference in the outcome of median number of days of hospitalization after randomization, from 14 days to 12 days, with a power set at 90%, a significance of 0.05, and an attrition of 5%, the trial would require 587 infants per group for a total of 1174 infants. At 80% power, the trial would require 479 infants per group for a total of 878 infants. The minimum required sample size for this trial will be 878 (439 in each treatment group), but enrollment will continue until either the presently-acquired supply of study drug is exhausted or expires in approximately August 2023 (accounting for full in-hospital and post-discharge follow-up), whichever comes first. The Neonatal Research Network gathers data on approximately 3000 moderately preterm infants a year, with approximately 1000 treated with caffeine.

Effect Size (days)	Significance	Power (%)	Attrition (%)	Sample Size
14 to 10	0.05	80	5	226
14 to 10	0.05	90	5	302
14 to 12	0.05	80	5	878
14 to 12	0.05	90	5	1174

SECTION 2. CONFLICT OF INTEREST DISCLOSURES

Per Title 42, Code of Federal Regulations, Part 50, Subpart F (50.604 Responsibilities of Institutions regarding Investigator financial conflicts of interest), as amended, institutions and all sub-recipients are required to notify the grants officer of any financial conflicts of interest (FCOI) prior to expenditure of any funds and within 60 days of any subsequently identified FCOI.

SECTION 3. STATEMENT OF PROBLEM

3.1. HYPOTHESES

3.1.1. Primary Hypothesis

The primary hypothesis is that in moderately preterm infants with resolved apnea of prematurity (AoP), continuing caffeine treatment compared to placebo will decrease the number of days of hospitalization from randomization to discharge up to 48 weeks post-menstrual age (PMA), with censoring at time of transfer or death. AoP is a leading cause of prolonged hospitalization in these infants and, therefore, it is expected that caffeine therapy will shorten hospitalization.

3.1.2. Secondary Hypotheses

In moderately preterm infants with resolved AoP, continuing caffeine therapy for 28 days after hospital discharge compared to placebo will:

a. decrease the number of days to reach physiologic maturity from randomization to discharge up to 48 wks PMA.
b. decrease the number of readmissions to the hospital related to apneic or apparent life-threatening events as well as all-cause readmissions within the first four weeks, second four weeks, and first eight weeks combined after discharge from the hospital by 48 wks PMA.
c. decrease the number of sick visits related to apneic or apparent life-threatening events as well as all-cause sick visits to urgent care, emergency rooms, or health care providers within the first four weeks, second four weeks, and first eight weeks combined after discharge from the hospital by 48 wks PMA.
d. be safe for continuing caffeine during the hospitalization and after discharge home without an increase in side effects or adverse events
e. decrease the number of days of hospitalization from randomization to discharge, leading to a hypothetical cost-savings as a financial benefit of the trial's intervention

3.2. SPECIFIC AIMS

3.1.3. Primary Specific Aim

To evaluate the effect of continuing treatment with caffeine citrate in the hospital on number of days of hospitalization from randomization to discharge up to 48 wks PMA, with censoring at time of transfer or death.

3.1.4. Secondary Specific Aims

a. To evaluate the effect of continuing treatment with caffeine citrate in the hospital on number of days to reach physiologic maturity from randomization to discharge up to 48 wks PMA.

b. To evaluate the effect of treatment with caffeine until 28 days after hospital discharge on all-cause readmissions to a hospital (including apneic and/or apparent life-threatening events) within the first 8 weeks after discharge by 48 wks PMA.
c. To evaluate the effect of treatment with caffeine until 28 days after hospital discharge on the number of all-cause sick visits to urgent care, emergency rooms, or health care provider's office (including apneic and/or apparent life-threatening events) within the first 8 weeks after discharge by 48 weeks PMA.
d. To evaluate the side effects and adverse events of caffeine continuation in the hospital and after discharge up to 4 weeks post study drug administration.
e. To assess the hypothetical cost-savings by the reduction in number of days of hospitalization as a financial benefit of the trial's interventions.

3.3. BACKGROUND

AoP is a common diagnosis in moderately preterm infants, most exhibiting clinical signs of AoP as defined by the American Academy of Pediatrics [cessation of breathing for ≥ 20 seconds or < 20 seconds if accompanied by bradycardia and/or cyanosis in infants <37 weeks gestational age (GA)][1]. Moderately preterm infants comprise one fourth of NICU admissions[2,3]. In a retrospective cohort study of moderately preterm infants, 92% (23/25) were diagnosed with AoP at 30 weeks post-menstrual age (PMA). Even at 33 weeks PMA, 48% (59/122) of infants had AoP[4], and apnea may persist beyond 37 weeks, even until ~44 weeks PMA[5,6]. PMA at the time of resolution of apnea is inversely proportional to the GA at birth[7,8]. Although respiratory maturation occurs with increased PMA[4], there is uncertainty regarding the range of PMA at which there is complete resolution of AoP. This uncertainty can delay discharge, as sufficiently mature respiratory control is one of the essential

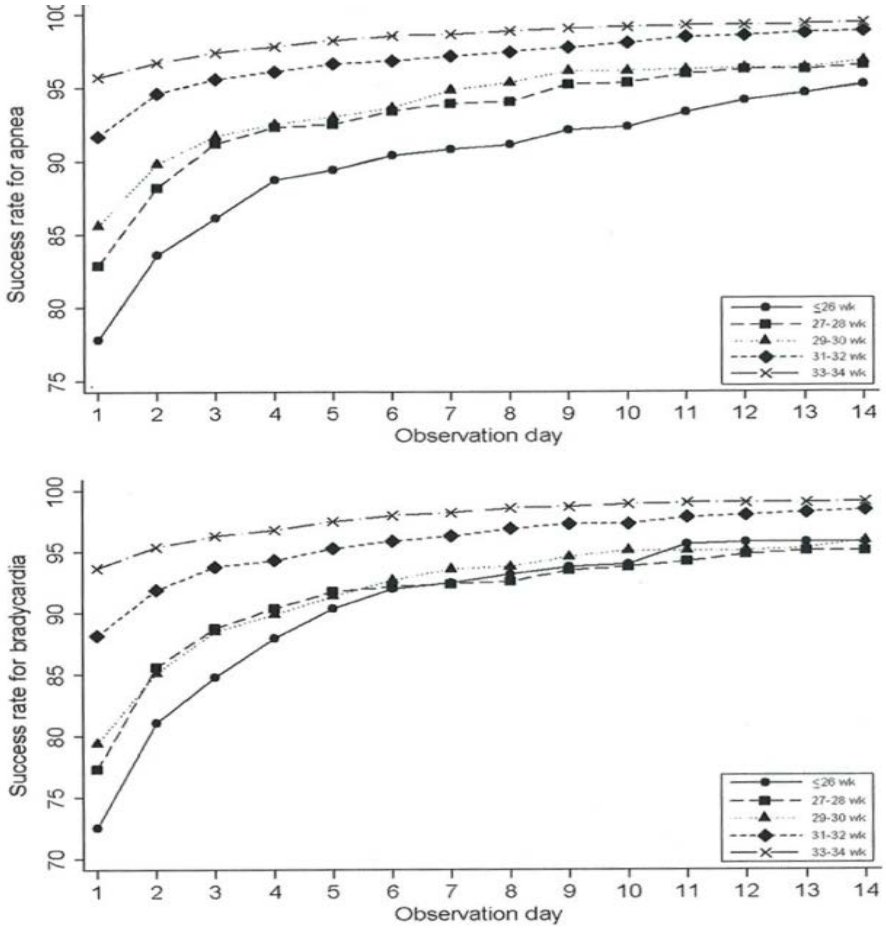

Figure 1. Lorch SA, Srinivasan L, Escobar GJ. Epidemiology of apnea and bradycardia resolution in premature infants. Pediatrics 2011;128:e366-73

physiologic competencies before discharge of the infant as recommended by the American Academy of Pediatrics[9].

There is wide variability in practice among physicians regarding the timing of discharge. In a retrospective study of discharge timing that included 435 infants born at 30 to 34 $^{6/7}$ weeks GA and admitted to one of 15 neonatal intensive care units, Eichenwald et al. noted that PMA at discharge ranged from 35.2 $\pm$ 0.5 weeks to 36.5 $\pm$ 1.2 weeks among the units despite similar criteria for discharge including full oral feeds, resolution of apneic episodes, and ability for thermoregulation[4]. In a large observational study, it was shown that even after infants had fulfilled other criteria for discharge, 15.8% (222/1403) of infants at 34 weeks' PMA had recurrent apneic episodes[7]. Although apneic episodes decrease even without treatment with caffeine, many infants continue to have apneas many days (observation day on Figure 1) after they are ready for discharge[7]. An intervention such as caffeine therapy that can decrease apneic episodes can potentially shorten the hospitalization of infants who are prone to apnea but otherwise ready for discharge. In a retrospective study of 164 infants, 41 (25%) were discharged with caffeine citrate continued at home[10]. The authors did not report any deaths or adverse events[10]. In addition, home caffeine therapy may reduce the number of apneic episodes at home, some of which can lead to readmission to the hospital or sick visits to the emergency room, urgent care, or health care provider.

For many years, methylxanthines, primarily caffeine citrate, have been used to treat AoP[11,12]. Caffeine acts by inhibiting two of four adenosine receptors[13,14] stimulating the infant to breathe and reducing apneic episodes[12]. Furthermore, methylxanthines improve function of the respiratory musculature, including increased diaphragmatic contractions[15-17]. In multiple trials, methylxanthines have been shown to reduce AoP[11,18]. Caffeine decreases obstructive, central, and mixed apnea [19]. A recent Cochrane review of five randomized controlled trials that included a total of 192 preterm infants indicated that methylxanthine treatment for apnea resulted in less treatment failures compared to placebo [RR 0.44 (95%CI 0.32 to 0.60), NNT 3 (95%CI 2 to 4)] as well as a decreased use of intermittent positive pressure ventilation [RR 0.34 (95% CI 0.12 to 0.97), NNT 13 (95% CI 6 to 100)][18]. Tachycardia was the only side effect that was more common in the caffeine group[18]. A double-blind placebo-controlled trial showed that weight gain did not differ between intervention and placebo groups[19]. In addition, a large randomized placebo-controlled trial of prolonged treatment with caffeine in extremely preterm infants showed short and long-term benefits of caffeine without evidence of side effects[11,20].

Three retrospective cohort studies of caffeine treatment at home for infants at risk for apnea and infants with apnea of infancy have been reported[10,21,22]. The median PMA at last dose of caffeine was 34.4 weeks in a large clinical trial[11] while in another large multicenter study, the average PMA at discharge was 35.7 weeks (encompassing infants born at 30 to 33 weeks GA). This illustrates many infants continue to receive treatment late in their hospital course. As apnea can still occur past these PMAs, continuing caffeine beyond the usual duration of treatment through hospital discharge may decrease late episodes of apnea that occur in the hospital. Often, these late apneas can prolong hospital stay due to an additional period of monitoring for further apnea. In addition, continuation of caffeine beyond hospital discharge may prevent complications from AoP that lead to hospital readmission or unplanned healthcare visits. A trial investigating the use of prolonged caffeine citrate treatment would provide high level of evidence and generalizability

to determine the effects on length of hospitalization, readmissions, and sick visits in moderately preterm infants. The proposed trial will evaluate infants for eight weeks following discharge, since infants would have reached at least a PMA of 40 to 44 weeks at the end of the evaluation period. Thus, the number of events of apnea and bradycardia should not differ when compared to full term infants of the same PMA[8,15,23]. This is the reasoning for the eight week evaluation period following hospital discharge.

3.4. Justification for the Study

Moderately preterm infants represent a relatively large group of neonates who require admission to the NICU, but discharge can be delayed by AoP or other factors. According to the American Academy of Pediatrics guidelines for hospital discharge of preterm infants, infants must have sufficient respiratory control before discharge[9], yet half of preterm infants were found in one study to continue to have apneic episodes at 33 weeks PMA[2]. According to a study by Eichenwald et al. apnea was one of the two most common factors responsible for prolonging hospitalization[4]. Historically, there has been a fear of discharging preterm infants home too early, as they are at increased risk for continued AoP at home and potentially may experience an apparent life-threatening event[21] requiring an emergency room visit and readmission related to apneic and bradycardic events after discharge. Caffeine treatment is effective in decreasing the episodes of apnea[11,18]. The current practice is to discontinue its use before discharge and evaluate for development of apneic episodes but this trial could change this paradigm and shorten hospitalization in a safe way by continuing caffeine treatment beyond discharge home.

Apneic episodes frequently recur after discontinuation of caffeine treatment. Hypothetically, continuation of caffeine after resolution of apneas would prevent further apneas and allow for earlier discharge from the NICU, if other competencies of physiologic maturity have been achieved, including temperature regulation and feeding tolerance. Complete maturation of the respiratory center does not occur until as late as 44 weeks in preterm infants[8]. As the average age of discharge of moderately preterm infants is between 35 to 37 weeks[4], apnea may still occur after discharge. Home therapy with caffeine can potentially decrease re-admissions to the hospital or sick visits due to AoP. To test these hypotheses, a randomized placebo-controlled trial of caffeine is proposed. The aim of this trial is to determine if continuing treatment with caffeine citrate in the hospital in moderately preterm infants with resolved apnea of prematurity instead of discontinuation of treatment in the hospital decreases hospital days. We will also determine if continuing caffeine at home decreases apneic episodes that may occur after discharge. The results of the trial could potentially transform how AoP is managed in moderately preterm infants during hospitalization as well as following discharge.

A trial of continuing and discharging infants on home caffeine therapy is novel, but in several small retrospective reviews[10,21,22] and a multicenter observational study[4], a minority of the infants were discharged on methylxanthine treatment. However, there are no data on the effectiveness and safety of late hospital and home methylxanthine treatment. The proposed trial will be the first of its kind and will help determine if this management strategy is beneficial and safe.

To be able to carry out this multicenter trial, there is need to enroll a large number of moderately preterm infants. Approximately 3000 preterm infants of this gestational age group are admitted a year to the NRN NICUs, with approximately one-third receiving caffeine treatment. Given the vast experience of the study-site principal investigators in multicenter trials as well as the research infrastructure, with research nurses and pharmacists, we believe that the NRN is particularly suitable to successfully perform this multicenter trial.

Potential challenges in performing this trial include:

a. The administration of study medication at home by the parents without frequent missed doses
b. Loss to follow up
c. Inaccurate or missing information regarding re-admission to the hospital or to sick visits
d. Inaccurate data collection on follow-up forms provided by the parents
e. Side effects from the study medication

The trial will be approved by each institutional review board (IRB). Parental consent will be obtained for each infant enrolled. Safety is of upmost importance and will be monitored by the Data Safety Monitoring Committee (DSMC) when 25%, 50%, and 75% of the subjects complete the eight-week follow up period (or are lost to follow up). The trial will record side effects and adverse events will be reported to the DSMC periodically. Expedited serious adverse events will be reported per local IRB guidelines and to the NICHD and NRN Data Coordinating Center at RTI.

SECTION 4. STUDY DESIGN

4.1. PRIMARY OUTCOME

The primary outcome of the study will be the number of days of hospitalization from randomization to discharge up to 48 weeks PMA, with censoring at time of transfer or death.

4.2. SECONDARY OUTCOMES

The secondary outcomes of the study will be:

a. The number of days to physiologic maturity after randomization up to 48 wks PMA. Physiologic maturity will be defined as follows:
   i. Temperature: out of the incubator for at least 48 hours with normal body temperature
   ii. Feeding: oral feeding at a volume of at least 140 ml/kg for 48 hours or growing on less than 140 ml/kg/day for at least 48 hours
   iii. Respiratory: apnea-free for at least 5 consecutive days

b. Post-menstrual age (PMA) at discharge up to 48 wks PMA, censoring at time of transfer or death (status).
c. The number of all-cause readmissions, including apneic events and apparent life-threatening events (ALTE), to the hospital within the first four weeks, second four weeks, and first eight weeks combined after discharge from the hospital by 48 wks PMA.
   An apparent life-threatening event is defined by the American Academy of Pediatrics as an event that is perceived by the observer as life-threatening. This event can include apnea, color change (cyanosis), profound change in muscle tone (hypotonia), gagging, and/or choking[24].
d. The number of all-cause sick visits, urgent care, emergency rooms, or health care provider's office, within the first four weeks, second four weeks, and first eight weeks combined after discharge from the hospital by 48 wks PMA.
e. Safety measures pre-hospital discharge
   a. Weight gain from randomization until status (discharge up to 48 wks PMA, with censoring at time of transfer or death). The weight gain may also be assessed using percentiles including birthweight percentiles.
   b. The number of days after randomization until status that infant had at least two consecutive heart rates >200 documented at least 3 hours apart (when infant not crying).
   c. Treatment for high blood pressure initiated after randomization until status.
   d. The number of episodes between randomization and status that infant was placed NPO for ≥ 24 hours.
   e. The use of anti-reflux medications started between randomization and status
   f. The number of days that significant apnea/bradycardia, as defined by documentation of infant receiving any of the following between randomization and status: open label caffeine, other methylxanthines, doxapram, CPAP or ventilatory support for apnea/bradycardia.

g. The presence of documented and treated arrhythmias between randomization and status, not due to tachycardia or bradycardia.
h. The onset of documented seizures, as defined by treating with anti-convulsants, between randomization and status

f. Death

Apnea of prematurity (AoP) is defined by the AAP as cessation of breathing for ≥ 20 seconds or < 20 seconds if accompanied by bradycardia and/or cyanosis in infants <37 weeks GA[24]. However, individual study sites may vary in its definition, and for purposes of the study the diagnosis of AoP will be determined by the attending neonatologists in each hospital (apnea countdown as per local practice pre-specified for each hospital) and by the attending neonatologist on each specific infant. For the purposes of this study, significant apnea episodes are defined as apnea events receiving treatment ordered by the attending physician (e.g. re-starting caffeine, not just stimulation for example).

Evaluation of infants during the first four weeks, second four weeks, and first eight weeks combined after discharge from the hospital is done to determine whether there is a difference in secondary outcomes on caffeine (first four weeks after discharge), off caffeine (second four weeks after discharge), and in overall outcomes after discharge home (first eight weeks after discharge).

A short discussion on the hypothetical cost-savings by the reduction in number of days of hospitalization as a financial benefit of the trial's intervention (caffeine versus placebo) will be done at the conclusion of the trial.

4.3. STUDY INTERVENTION

We propose enrolling moderately preterm infants who are between 33 $^{0/7}$ and 35 $^{6/7}$ weeks GA (inclusive) who are being treated with caffeine for AoP and for whom plans are to discontinue caffeine. Once the infant has been screened for eligibility, consented, and the neonatologist has determined that caffeine will be stopped, infants will be eligible to be randomized if they can be started on the study medication within 72 hours after stopping caffeine. They will be randomized either to continuing caffeine citrate at a dose of 10 mg/kg/dose (5 mg/kg caffeine base) given daily (treatment group) or an equal volume of placebo given daily (placebo group), not less than 12 hours between doses, to continue during the hospital stay and for 28 days after hospital discharge. In-hospital dosages will be adjusted weekly based on weight. Post-discharge dosage will be based on weight obtained within 48 hours of discharge.

Trial Arms		Trial Intervention
Intervention Group	Caffeine	Caffeine citrate 10 mg/kg/day given once daily until 28 days after discharge
Control Group	Placebo	Placebo contains all of the excipients except for the active ingredient, caffeine citrate (a volume equivalent to 10 mg/kg of caffeine citrate) given once daily for 28 days after discharge.

The trial medication (caffeine citrate or placebo) will be weight-adjusted on a weekly basis until discharge. An apnea countdown will be done as per local practice before discharge. The duration of this countdown will be site dependent but pre-specified. Many infants may require hospitalization for observation after resolution of the apneas because of other discharge issues such as temperature control or feeding tolerance. If the attending neonatologist decides that re-initiation of open-label caffeine is clinically indicated, caffeine/placebo treatment per randomization will be put on hold until the physician decides to discontinue open label caffeine at which time, the infant will be treated as per randomization within 24-72 hours after open label caffeine is stopped. Infants on study medication who are still in the hospital at 44 weeks PMA will have the caffeine/placebo discontinued.

Prior to discharge, a weight obtained within the last 48 hours will be used to determine the post-discharge dosage for those infants continuing with caffeine citrate or placebo at home. Once deemed ready for discharge, the parent will be supplied with 28 numbered vials with oral caffeine citrate (intervention group) or placebo at an equivalent volume (placebo group). The parents will be educated by the research nurse, discharge nurse, physician, or pharmacist on storage and administration of study medication. Infants will be continued at home on the same dose of caffeine citrate or placebo for the first 28 days after hospital discharge. A member of the research team will contact the parents to obtain post-discharge information within 72 hours after discharge, once a week for the first 4 weeks, and biweekly during the weeks 5 to 8 after discharge.

4.4. BLINDING/MASKING

Caffeine citrate therapy or placebo, depending on the randomized treatment allocation, will be prepared by the study pharmacist for administration in the NICU. Study pharmacist will prepare daily doses of study drug (caffeine or placebo) for administration while in the hospital. At discharge, study pharmacist will dispense a 28-day supply of either caffeine or placebo vials for home administration. All other research staff and all health care staff and family members will be blinded to the treatment allocation. The study medication can be prepared by the research pharmacist within 48 hours of anticipated discharge date.

4.5. POTENTIAL RISKS AND BENEFITS TO SUBJECTS

4.5.1. Current Standard of Care

AoP is quite common in premature infants; 50% to 90% of infants with GA in the range of the proposed trial have AoP[4]. A review of 100 infants in the NICU at University of Alabama at Birmingham showed that 37% of infants within this cohort were treated with a methylxanthine. This is similar to Neonatal Research Network data from the Moderately Preterm Cohort Study, which showed that approximately one-third of infants received caffeine therapy. AoP can lead to intermittent hypoxemia, and if prolonged, can precipitate bradycardia and hypotension, which may lead to hypoxic-ischemic neurological injury[25,26].

Initiating Caffeine Therapy

Currently, infants of 29 $^{0/7}$ to 33 $^{6/7}$ weeks GA at birth are admitted to the NICU. There is some variation in the practice of treatment with caffeine for preterm infants. Caffeine treatment may be started prophylactically upon admission for some preterm infants. Data from the Cochrane meta-analysis showed no differences in outcomes between prophylactic caffeine and placebo[12]. Another practice is to administer caffeine in preparation for extubation. This method was shown to reduce extubation failure (RR 0.48, 95% CI 0.32 to 0.71) within a week[27]. In general, multiple studies have shown the benefit of caffeine therapy in decreasing apneic episodes[11,12,18,25-27]. Therefore, the common practice is to give caffeine treatment to preterm infants who have apnea thought to be due to prematurity.

Discontinuing Caffeine Therapy

There is a wide variation in practices for discontinuing caffeine therapy. Caffeine has a half-life of approximately 4 days (~100 hours) in preterm infants[28,29]. After an infant no longer has apneic episodes for a variable amount of time, neonatologists opt to discontinue caffeine. Most neonatologists will observe infants in the hospital for at least five days following discontinuation of caffeine treatment, and this has been incorporated into this trial protocol.

Discharge Home

The American Academy of Pediatrics guidelines deem preterm infants ready to be discharged once they have achieved three main competencies: the ability to grow on full oral feeds, the ability to maintain body temperature in a simulated home environment, and sufficient maturity of respiratory control to allow for safe discharge[9]. However, even with these guidelines, there is still a wide variety of practice regarding discharge. In addition, although most infants have caffeine discontinued, there is still a subset of infants that are discharged home on caffeine. In a multicenter study by Eichenwald et al, 6% of infants aged 30-33 weeks PMA were discharged on methylxanthine treatment[4]. This trial will help answer whether the practice of discharging moderately preterm infants on caffeine shortens hospitalization and reduces readmissions and sick visits and whether other aspects of physiologic maturity are responsible for delays in discharge.

4.5.2. Risks

Neofax, a pharmaceutical reference source, includes side effects of caffeine citrate such as vomiting and restlessness, as well as functional cardiac symptoms, all based on low level of evidence studies[32]. In two randomized-controlled trials, the frequency of side effects between infants receiving caffeine and those in the placebo group did not differ[11,19]. Data on these measures are not collected usually in clinical care or trials so we will not collect them.

In the largest caffeine trial to date, the Caffeine for Apnea (CAP) trial, decreased weight gain was reported in the caffeine group as compared to the placebo group in the first days of treatment. However, weight gain during the hospitalization did not differ between caffeine and placebo group infants[11]. In a recent large, randomized controlled trial of high-dose (caffeine

citrate 20 mg/kg, twice the dose planned for this trial) versus normal-dose caffeine (caffeine citrate 5 mg/kg), tachycardia was more frequent but still relatively uncommon occurring in 4% in the high-dose group. There was no difference in any other adverse effects between groups including feeding intolerance despite the use of doses much higher than those that will be used in the current trial[33]. Serious toxicity has been noted in patients who have inappropriately received overdoses of caffeine with blood levels exceeding 50 mg/L[34] but are rare with correct dosing. The most recent Cochrane meta-analysis did not include an analysis of side effects related to the use of methylxanthines[12].

A small study of 16 premature infants evaluating the effects of caffeine citrate on cerebral blood flow showed that giving high doses (25 mg/kg/day; base 12.5 mg/kg caffeine) decreased cerebral blood flow as measured from the internal carotid artery, with a reduction of 17 % and 22% at 1 hour and 2 hours post administration of caffeine, respectively[10]. Another study corroborated the findings of decreased cerebral blood flow with high doses but showed that at a dose of 10 mg/kg/day or less of caffeine citrate there was no effect on cerebral blood flow[35]. The large Caffeine for Apnea trial which used doses up to 10 mg/kg/day showed that neurodevelopmental impairment was reduced with caffeine treatment[21]. The proposed trial will be using caffeine citrate doses of 10 mg/kg/day so there is no concern regarding alteration of cerebral blood flow.

Premature infants are being discharged at an average PMA of approximately 36 weeks, according to a large multicenter study[4]. Although the majority of infants have resolution of apnea by 40 weeks PMA, some studies suggest late resolution of apneas, up to approximately 44 weeks PMA (accounting for maturation of the respiratory center)[5,6]. There is a possibility that sub-clinical apneic episodes may occur at home and could potentially lead to re-admissions to the hospital or sick visits. This risk will be evaluated as a secondary outcome in the proposed trial.

The review of the literature did not show increased risk of death from administration of caffeine citrate[11,18]. Infants enrolled in this trial will have the timing of discharge determined by the attending neonatologist. The trial will not deviate from the local practices in determining discharge criteria or discharge timing.

Infants that qualify for this study are at increased risk for death, disability, and/or poor neurodevelopment given their underlying prematurity. They are also at risk for developing other conditions related to prematurity including but not limited to apnea, bradycardia, respiratory distress syndrome, intracranial hemorrhage, retinopathy of prematurity, feeding intolerance, infection, and bronchopulmonary dysplasia. These are existing risks of prematurity regardless of whether they participate in this study or not.

We do not anticipate an increase in the risk of death or adverse outcomes for infants receiving either of the treatments provided in this study over and above those risks seen historically in similar infants. There may, however, be other unknown serious risks or risks associated with being in this study that we do not anticipate at this time.

Infants and their families may experience stress and emotional distress from their time in the NICU and participation in the trial. There is a potential loss of confidentiality should the patient information be lost, stolen, or inadvertently distributed.

4.5.3. Benefits

The American Academy of Pediatrics Committee on Fetus and Newborn supports a shorter hospital length of stay, as it benefits the family and infant, allowing for less separation as well as possibly decreasing the risk for hospital-acquired infections[9]. However, due to the uncertainty in the timing of resolution of apneic episodes in preterm infants, it is challenging for neonatologists to know when to discontinue caffeine and discharge patients home. A common problem is that even after infants have fulfilled other criteria for discharge, such as thermoregulation and full oral feeds, apnea may still be present and can prolong hospitalization, as was illustrated in a study where 15.8% (222/1403) of infants at 34 weeks' PMA continued to have recurrent apneic episodes as the only reason for remaining hospitalized[7].

A potential benefit of trial participation and randomization to the Caffeine arm is that there may be fewer episodes of apneas in the NICU and the infant may be able to be discharged home earlier than those infants who receive placebo. This decreases the time that parents are stressed with a hospitalized infant as well as potentially decreasing the risk of intra-hospital acquired infections. In addition, with the administration of caffeine at home, there is the possibility of reducing apneic episodes that could lead to readmissions to the hospital or require sick visits to the health care provider, urgent care, or emergency room with further evaluation with x-rays and blood sampling. Also, the Caffeine for Apnea trial showed the benefits of caffeine use as it relates to patent ductus arteriosus, with a reduction in both medical (29.3% vs. 38.1%) and surgical (4.5% vs. 12.6%) treatment [11].

Another potential benefit of the proposed trial would be the reduction of intermittent desaturation events in the infants continuing caffeine treatment. Intermittent desaturations, regardless of apneic episodes, may be related to neurodevelopmental impairment in premature infants[36,37] as well as the development of retinopathy of prematurity[38]. A recent small randomized controlled trial compared the use of prolonged caffeine citrate versus no caffeine in infants between 34 and 37 weeks GA to reduce intermittent desaturations. Infants of 35 weeks and 36 weeks GA in the caffeine group had a reduction in episodes of desaturations below 90% by 52% (95% CI, -70% to -22%) and 46% respectively (95% CI, -65% to -11%)[39] but there was no reduction in desaturations from 37 weeks and beyond.

This trial is testing caffeine treatment, which is used in NICUs throughout the world, with the main difference being the timing of discontinuation of treatment. As such, the subjects may receive no direct benefit from participating in this study.

Infants receiving one treatment may have improved outcomes over those seen in the other treatment group. We do not know which treatment group will or will not show improvement and it is possible that the outcomes will be the same for the two treatment groups.

SECTION 5. METHODS

5.1. STUDY POPULATION

5.1.1 Inclusion Criteria

Inborn and outborn infants of 29 $^{0/7}$ to 33 $^{6/7}$ weeks GA at birth and admitted to hospitals of the National Institute of Child Health and Human Development Neonatal Research Network ≤ 72 hours of age will be eligible if they meet all of the following inclusion criteria at time of enrollment:

a. 33 $^{0/7}$ - 35 $^{6/7}$ weeks PMA at the time of randomization
b. Receiving caffeine with plan to discontinue treatment or just discontinued caffeine treatment
c. Receiving full feeds (defined by a volume of ≥120 ml/kg/day) by oral and/or tube feeding
d. Ability to start study medication within 72 hours after stopping caffeine,

5.1.2 Exclusion Criteria

Any of the following criteria will exclude an infant from the trial:

a. On respiratory therapy (oxygen more than room air equivalent for high altitude sites, nasal cannula, continuous positive pressure ventilation, and/or mechanical ventilation)
b. Infants who would otherwise be discharged home on apnea monitor due to underlying disease or family history, including history of a sibling with sudden infant death syndrome
c. Parental request for apnea monitor
d. Congenital heart disease other than atrial septal defect, ventricular septal defect, or patent ductus arteriosus
e. Neuromuscular conditions affecting respiration
f. Major congenital malformations and/or genetic disorders
g. Plans to transfer to a non NRN site before discharge
h. Unable to obtain parental or guardian consent

5.2. DETAILED STUDY PROCEDURES

5.2.1. Screening and Consent

Initially, the research nurses, coordinators, and physicians will identify all infants born between 29 $^{0/7}$ and 33 $^{6/7}$ GA at birth. Consent can be obtained at any time. Evaluation for enrollment in the trial will be done once there are plans to discontinue caffeine treatment and the infant is between 33 $^{0/7}$ and 35 $^{6/7}$ weeks PMA (inclusive). Parents or a legal guardian of the infant who meets all the inclusion criteria and does not meet any of the exclusion criteria will be approached by the research nurse, coordinator, and/or physician for written informed consent. Infants who are deemed to require apnea monitoring at home after enrollment has occurred will be allowed its use and this will be noted on the Follow-up form.

5.2.2. Randomization Procedures

When the attending neonatologist has discontinued clinical caffeine on an eligible and consented infant that is 33 $^{0/7}$ - 35 $^{6/7}$ weeks PMA, the infant can be randomized if it is possible to start study medication within 72 hours after stopping caffeine.

Infants will be randomized 1:1 using a stratified permutated block design with a centralized procedure. Infants will be stratified by study center into two GA groups; infants born at 29 to 30 $^{6/7}$ weeks GA and 31 to 33 $^{6/7}$ weeks GA. Randomization will occur through the Data Coordinating Center of RTI International (Research Triangle Park, North Carolina). Treatment allocation will be revealed only to the research pharmacy staff, who will prepare either caffeine citrate at 10 mg/kg (base of 5 mg/kg) or an equivalent volume of placebo to be administered once a day. The dosage will be based on the weight closest to randomization and then adjusted weekly for weight. Because both caffeine and placebo are colorless, they are indistinguishable and, therefore, blinding will be accomplished for all care providers and research staff.

The oral delivery should begin as soon as clinically possible.

Randomization of twins and higher order multiples (when eligible) will be done separately.

5.2.3. In-hospital Procedures

Study subjects are infants in the NICU at one of the principal or associated sites of the NRN. Once the attending physician has discontinued caffeine therapy, the infant will be randomized as described in section 5.2.2. The research pharmacist will be notified of enrollment and the infant will receive a once-a-day dose of caffeine citrate at 10 mg/kg/dose (5 mg/kg caffeine base) as part of the treatment group or receive placebo at the same volume and time every 24 hrs and not given less than 12 hours apart. The doses will be weight adjusted on a weekly basis. If the infant is later put NPO, the oral caffeine citrate or placebo will be held until feeding resumes and at the discretion of the attending neonatologist.

In-hospital apnea and bradycardia events will be monitored using individual study site monitor devices. There are no universal definitions for apnea and bradycardia and therefore, diagnoses of these will be left at the discretion of each hospital group of neonatologists (pre-specified) and the neonatal team caring for the infant. The data on apnea and bradycardia will be used to determine physiologic maturity and for the local decision about discharging the babies home. The definitions of apnea and bradycardia will be decided locally. However, for the purposes of this study, significant apnea/bradycardia will be defined as apnea/bradycardia events receiving treatment. Treatment is defined as ordered by the attending physician (e.g. re-starting caffeine, not just stimulation for example). Using local definitions will increase generalizability and interfere less with local decision making.

Data will be collected from the infant's electronic or physical chart. The number of infants who receive CPAP, mechanical ventilation, and/or open label caffeine, other methylxanthine or doxapram for the treatment of apnea/bradycardia after randomization will be noted for the study.

The protocol will allow for individual study site centers to use their own discharge criteria, but for the purposes of the definition of secondary outcome of the trial, infants must have reached physiologic maturity, which includes a) out of an incubator for at least 48 hours, b) oral feeding at volume of at least 140 ml/kg/day or growing on less than 140 ml/kg/day for at least 48 hours, and be apnea-free for at least 5 consecutive days. Infants who are still in the hospital at 44 weeks PMA will have the study medication (caffeine/placebo) discontinued. Analysis will be done by intention to treat. If an infant is discharged before meeting the definition of physiologic maturity, it will be noted for analysis at the conclusion of the trial. The weight within 48 hours of discharge will be used for the caffeine/placebo home administration. The dose will not be adjusted for weight gain after discharge. The practice of discharging infants home on open-label caffeine will not be a part of the trial. However, should it occur, it will be noted as a protocol deviation and will be noted for subsequent analysis.

Prior to discharge, a research nurse, physician, or pharmacist will educate the parents on storage and administration of the medication to the infant. Other instructions to the parents include preparation of daily dose and if a dose is missed, it may be given at any time on that day if the dose can be given at least 12 hours before the next day's dose is due. If it was not given at all, the parents will be instructed to discard the entire vial that was missed and record it on the medication form. If an infant spits or vomits after a dose is given, another dose should not be given on the same day. Follow-up forms (Medication and Follow up Forms) will be supplied to allow the parents to keep track of daily medication administration and missed doses. The parent will be given a stamped envelope to return the forms to the NRN research coordinator at the end of the 8 weeks. If the study site allows for the use of a gift card, it will be mailed to the parent or guardian when the documents are returned to the research coordinator. The gift card will encourage the family member to return the follow up documents at the end of the 8-week follow up period. Because it will be supplied at the end of the study period, it will have no consequences to the enrollment or treatment of the infant. In addition, the gift card does not constitute payment to the family member for any service provided as part of the trial.

Of note, infants who are deemed to require apnea monitoring at home after enrollment will be allowed its use and this will be noted on a follow-up form. Data from the home monitor recordings will not be used in the trial.

The NRN research coordinator and staff will obtain maternal demographics data including age, race, education, marital status, and parity. In addition, infant data will also be recorded, including weight at birth, randomization, and status; length/head circumference at birth and status; date of status; date of last apnea episode recorded after randomization; use of CPAP or mechanical ventilation; date of last NPO episode lasting >24 hours as well as the number of episodes of NPO >24 hours following randomization; date of last orogastric or nasogastric feed; date of last day in incubator; dates of initiation and termination of open label caffeine therapy; and information related to side effects and adverse events.

5.2.4. Post-hospital Procedures

Following discharge, the research team will contact the family within 72 hours after discharge, once a week for the first 4 weeks, and biweekly during the weeks 5 to 8 after discharge to ensure the study medication is being administered adequately and to gather information on doctor or hospital visits.

Parents will be given a Health Care Provider Letter. A copy will also be sent directly to the Health Care Provider's office. The letter will clearly describe the trial goals and procedures, the dose of the study medication, and PI contact information.

SECTION 6. ANALYTICAL PLAN

6.1. SAMPLE SIZE AND AVAILABILITY

To obtain a two-day difference in primary outcome of days from randomization to discharge, from 14 days to 12 days, with a power set at 90%, a significance of 0.05, and a 5% attrition, the trial would require 587 infants per group (intervention and placebo) for a total of 1174 infants, assuming a two-tailed non parametric test comparing median LOS in the two groups. With a power set at 80%, under the same assumptions and significance, the trial would require 439 infants per group for a total of 878 infants. The minimum required sample size for this trial will be 878 (439 in each treatment group), but enrollment will continue until either the presently-acquired supply of study drug is exhausted or expires in approximately August 2023 (accounting for full in-hospital and post-discharge follow-up), whichever comes first. There are approximately 3000 infants born between $29^{0/7}$ and $33^{6/7}$ weeks gestation per year in the NRN. A review of 100 infants in the NICU at one of the largest centers in the NRN showed that 37% of infants within this cohort were treated with a methylxanthine. This is similar to NRN data showing that approximately 1000 (one-third) of infants receive caffeine therapy.

Effect Size (days)	Significance	Power (%)	Attrition (%)	Sample Size
14 to 10	0.05	80	5	226
14 to 10	0.05	90	5	302
14 to 12	0.05	80	5	878
14 to 12	0.05	90	5	1174

6.2. STATISTICAL ANALYSIS PLAN

The primary analysis will compare number of days of hospitalization from randomization to discharge, death, transfer or 48 weeks PMA, whichever occurs first between the intervention and control groups using median regression controlling for study center and GA group (the two stratification factors for this trial). Likewise, the treatment effect for the secondary outcomes (number of days to physiologic maturity after randomization, number of readmissions and number of sick visits) will be compared using either median regression or a Poisson regression model controlling for study center and GA group.

Secondary analyses will evaluate whether other models better fit the distributions for these outcomes (for example, survival analysis models for the primary outcome and negative binomial or log linear models for the secondary outcomes).

We will examine treatment heterogeneity for the primary outcome by adding interaction terms between treatment and study center, as well as treatment and GA group. If any of these interaction terms are close to statistical significance ($p<0.1$), for treatment heterogeneity by study center, we will attempt to identify centers where the treatment effect may be different (although the statistical power available to conduct such analyses will be fairly limited). If there is

indication of treatment heterogeneity by GA group, we will conduct stratified analyses by GA group to quantify the treatment effect separately by GA group.

6.3. DATA MONITORING PLAN

6.3.1. Monitoring for Side Effects and Adverse Events

Any infant that develops side effects or minor adverse effects related to the intervention can be continued on study medication at the discretion of the attending physician but the event will be recorded for the trial. If the infant demonstrates tachycardia of 220 beats per minute for greater than 60 minutes, the clinical team should hold the study drug for 24 hours. If tachycardia resolves, the study drug may restart.

Enrolled infants will have their inpatient record reviewed by research coordinators to obtain the following data:

- Infant weight: at birth, day of randomization, and status
- Heart rate: Number of days after randomization until status that there were at least two consecutive heart rates documented over 200 bpm (when infant was not crying) at least 3 hours apart
- Treatment for high blood pressure initiated after randomization until status
- Gastrointestinal issues (NPO for more than 24 hours)
- Use of reflux medications at status

In the largest caffeine trial, the Caffeine for Apnea trial, initial decreased weight gain was reported in the caffeine group as compared to the placebo group but with continued caffeine treatment, long-term weight gain did not differ between caffeine and placebo group infants[11]. Differences in weight gain from the day of randomization, day of discharge (status), and at the infant's well child visits (e.g. one and/or four week periods discharge) will be monitored

Apnea/bradycardia:

The trial will allow for individual study sites to continue their standard practice, and the definition of AoP will be left at the discretion of the neonatology staff treating the infant. If an infant develops apnea, treatment will be left at the discretion of the attending neonatologist or institution. The etiology of the ensuing event and its management (e.g. CPAP, mechanical ventilation, sepsis) will be recorded. Apnea and bradycardia are common in eligible infants even with caffeine treatment and will not be considered serious adverse events.

Other complications of prematurity that are not likely to be related to the intervention will also be collected following randomization into this trial. These include development of necrotizing enterocolitis, intraventricular hemorrhage, periventricular leukomalacia, late onset sepsis, and severe retinopathy of prematurity.

In addition, the following data will be obtained from the family during follow-up calls and from returned mailed-in forms:

- Infant weights at all health care provider visits (well child and sick visits)
- Reasons for sick visits to the Health Care Provider, urgent care, or emergency room
- Reasons for admission to the hospital
- Final diagnosis when discharged from the hospital

A member of the research staff will be available during the day (8 am to 5 pm) for questions regarding the study medication and trial. If the infant requires medical attention, it should be addressed by the Health Care Provider or emergency medical care staff. The evaluating physician should treat the patient's medical needs, regardless of the involvement in the trial. Once the patient is stable, if the physician or parent/guardian requires further information related to the trial, a member of the research team may be contacted. Information obtained from the trial is unlikely to change the immediate care of the patient if sick.

Expedited serious adverse events will be reported per local IRB guidelines, and to the NICHD and NRN Data Coordinating Center at RTI.

The trial will record side effects and any study related serious adverse events will be reported to the DSMC periodically. Expedited serious adverse events will be reported per local IRB guidelines, and to the NICHD and the NRN Data Coordinating Center at RTI. All protocol deviations and violations will be reported.

The following detail describes the action to be taken for each adverse event below:

Arrhythmias and seizures

Both arrhythmias (excluding those due to tachycardia or bradycardia) and seizures will be considered serious adverse events. Seizures have been reported with overdoses of caffeine (multiple doses of 20 mg/kg or more)[10,16,17,19] and therefore would be unexpected. However, should seizures occur in the hospital, it will be evaluated and managed by individual study site policies or attending neonatologist. Infants whose medication is held or stopped based on decision made by the attending neonatologist will be included in the analysis as the design includes intention to treat analysis. Episodes of arrhythmia (excluding those due to tachycardia or bradycardia), seizure, and other unexpected, related serious adverse events will be documented for the results of the trial, and the outcome is to be reported to the NICHD and RTI.

Hospitalization, sick visit to urgent care, emergency room or health care provider's office related to apneic or apparent life-threatening event (ALTE)

Hospitalization, sick visit to urgent care, emergency room or health care provider's office related to apneic or apparent life-threatening event (ALTE) will be considered serious adverse events. Readmissions to the hospital and sick visits to urgent care, emergency rooms, or health care provider's office related to apneic or apparent life-threatening event (ALTE) within the first eight weeks after discharge from the hospital will be collected for the results of the trial, and the outcome is to be reported to the NICHD and RTI

Infants will be monitored prospectively while in the NICU. Interim efficacy and safety will be formally evaluated by the independent Data Safety Monitoring Committee as specified in detail in Section 6.3.3.2.

6.3.2. Monitoring Drug Adherence and Compliance

Adherence to medication regimens is affected in a multi-factorial manner. A review of 51 studies with 19 chronic diseases found a wide range of factors for lack of compliance, falling within categories of socioeconomic, patient-related, and therapy-related determinants[40]. The conclusion of this large systematic review points to the use of multiple methods to better attain compliance with medications at home.

For this trial, we will combine two recommended methods to assure adequate monitoring and improve compliance with medication administration:

a. While the infant remains inpatient, the medication will be administered by the nurse as directed and the research nurse will perform a chart review at least twice a week to ensure study medication is being received after randomization and prior to discharge.

b. After discharge:

i. A Medication form will be supplied to the parents. This will include a daily item to mark if medication was administered. In addition, parents can use this form to record sick visits to the Health Care Provider, emergency room, or hospitalizations as well as weights obtained during well-child or sick visits and missed doses of study medication. Any new medications prescribed will also be noted on this form.

ii. A Follow-up form will be supplied. This will be similar to the Medication form, but will be used during the second four-week period discharge and will not include a medication administration section. Safety outcomes (such as Health Care Provider, Emergency visits, and re-admissions to a hospital) will be recorded on this form also.

iii. A member of the research team will contact the parents within the first 72 hours after discharge to answer questions and assess medication compliance.

iv. A member of the research team will contact the parents once a week during the first 4 weeks and biweekly during weeks 5-8 to address concerns and evaluate medication compliance*. During this contact, the parents will be asked about any well or sick visits made to the health care provider, urgent care, emergency room, or hospital since the last contact and the reason for these visits.

*To assure both safety and compliance, vials will be marked with a number corresponding to the beginning day of medication to be administered at home. For example, the next day after discharge, the parent is to administer the study drug from the vial marked #1 by oral syringe. The following day, the vial marked #2 should be given. This procedure, using an oral syringe, should be followed until day 28 after discharge when the last medication vial marked #28 should be

given. If a dose is missed, it may be given at any time on that day as long as it is given at least 12 hours before the next dose is due the next day. If it was not given at all, the parents will be instructed to discard the dose that was missed and record it on the medication form. The schedule of medication administration will then continue with the next numbered vial. This information will be noted for further analysis at the conclusion of the trial. Because of the long half-life of caffeine, single missed doses will have little clinical effect.

6.3.3. Statistical Interim Monitoring and Stopping Rules

Statistical interim monitoring for this trial will be conducted by the independent Data Safety and Monitoring Committee using data and analyses provided by the NRN Data Coordinating Center at RTI. We recommend that the Data Safety and Monitoring Committee meet formally to review interim safety, efficacy and futility, as well as other aspects of accruing data (such as enrollment, data completeness and protocol compliance) four times during the study, after 100 infants complete the eight-week follow up and then roughly after 25%, 50% and 75% of subjects complete the eight week follow up. Formal Data Safety and Monitoring Committee reports will be prepared by the Data Coordinating Center for these meetings. These reports will include the following information:

- Brief summary of the trial design, including primary and secondary hypotheses and outcomes, study population, inclusion and exclusion criteria, recruitment, screening, randomization and study intervention procedures, and statistical considerations for trial design and analysis
- Interim monitoring plan
- Enrollment, including screening, consent, randomization and study exit
- Completeness of data and edit queries. Baseline study population characteristics, overall and by treatment group
- Drug adherence and compliance
- Primary efficacy outcomes by treatment group
- Secondary efficacy outcomes by treatment group
- Safety outcomes, including death, by treatment group
- Protocol deviations and violations, overall and by treatment group.

These Data Safety and Monitoring Committee reports will be blinded, with treatments labeled as group A and group B. As per the NRN Data Safety and Monitoring Committee Charter, the DSMC may, however, request to be un-blinded to perform their duties. If the Data Safety and Monitoring Committee recommends modification or cessation of the study protocol due to safety concerns, NIH will make the final determination.

<u>Interim Safety Monitoring</u>
Statistical interim safety monitoring will be conducted by the DCC after 100 infants complete the eight-week follow up and then after 25% (300), 50% (600), and 75% (900) of the infants enrolled complete the eight-week follow up period. Formal safety assessment will be based on the number of sick visits, emergency room visits, apparent life-threatening event episodes or hospitalizations related to AoP. Relatively liberal Pocock safety bounds based on 5 interim safety looks at the data will be constructed to guard against any occurrence of false positives while at

the same time allowing for stopping at reasonable levels of evidence. Thus, at each of these safety looks, an increased incidence of the above safety events in the Caffeine group with $p < 0.0158$ will be considered as statistically significant evidence of harm that the Data Safety and Monitoring Committee can use to recommend suspension of the trial for safety reasons. In addition to the formal safety outcome, other safety outcomes collected in this trial (see section 6.3.1) will also be examined by treatment group. If a death occurs in either of the groups, the Data Safety and Monitoring Committee will review the cause of death and determine if the cause is linked to the study intervention. If it is deemed to be related to the intervention as an increased risk, the Data Safety and Monitoring Committee may recommend stopping the trial. After the Data Coordinating Center conducts each of these interim safety analyses, it will inform the Chair of the Data Safety and Monitoring Committee (or her designee) if there is any suggestion of a trend in the safety data. The Data Safety and Monitoring Committee Chair will then determine any future course of action, including convening a meeting of the entire panel to discuss the safety data.

Interim Efficacy Monitoring

Statistical interim efficacy monitoring will be conducted by the Data Coordinating Center after 25%, 50% and 75% of the babies enrolled into the trial complete eight-week follow up period. At each of these interim looks, the primary outcome will be compared by (blinded) treatment group as per the analysis plan in section 6.2. O'Brien Fleming stopping bounds for efficacy will be used to preserve an overall Type-I error rate of 0.05 for the primary outcome. Thus, stopping bounds for efficacy will be established if $p < 5 \text{ X } 10^{-5}$ at 25%, $p < 0.004$ at 50% and $p < 0.018$ at 75% of interim data accrual. In the event that these stopping bounds are reached, the Data Safety and Monitoring Committee may recommend termination of the trial for efficacy. In addition to the primary outcome, secondary efficacy outcomes collected in this trial (see section 4.2) will also be examined by treatment group.

Interim Futility Monitoring

Statistical interim futility monitoring will be conducted by the Data Coordinating Center after 50% and 75% of the babies enrolled into the trial complete the eight week follow up period. At each of these two looks, we will estimate conditional power, i.e., the probability to detect a statistically significant treatment effect for caffeine, given the observed data and the hypothesized treatment effect for the unobserved data. The Data Safety and Monitoring Committee may recommend suspension of the trial for futility if this probability is less than 15%. In addition to the conditional power analysis, the Data Safety and Monitoring Committee may also consider other pertinent aspects included in the interim report such as the quality of the data, protocol violations and treatment adherence, rate of enrollment, rate of attrition, in determining futility.

SECTION 7. FUTURE DIRECTIONS

This randomized, placebo-controlled, double-blinded, multicenter trial will inform us whether giving caffeine citrate throughout hospitalization will allow for decreased length of hospitalization of moderately premature infants as designed by an explanatory research method. The careful control of research subjects and variables in ideal conditions allows for efficacy in

clinical research. Possible future plans for this trial would be to determine if there are any differences in the neurodevelopmental outcomes at 22-26 months corrected age and at 5 years of age related to the use of prolonged caffeine at home in moderately preterm infants.

SECTION 8. DATA SHARING

Data collected for this study will be analyzed and stored at the Data Coordinating Center, RTI International. After the study is completed, the de-identified, archived data will be transmitted to the NICHD Data and Specimen Hub (DASH), for use by other researchers including those outside of the study. Permission to transmit data to DASH will be included in the informed consent.

SECTION 9. DATA FORMS

9.1. Screening Log
9.2. Eligibility and Consent Form
9.3. Randomization Form
9.4. Baseline Form
9.5. In-hospital Study Drug Administration Form
9.6. Open Label Treatment for Apnea Form
9.7. Pharmacy Drug Accountability Form
9.8. In-hospital Outcomes Form
9.9. Adverse Events Form
9.10. Protocol Deviation/Violation Form (S) – Masked and Unmasked Staff
9.11. Post-discharge Study Drug and Medical Visit Form
9.12. Post-discharge Status Form

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