NICHD
NEONATAL RESEARCH NETWORK

Moderately Preterm Infants Discharged with Caffeine at Home for Apnea: The MoCHA Trial

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NIH Eunice Kennedy Shriver National Institute of Child Health and Human Development

Disclosures

- Speaker: Wally Carlo

- Dr. Carlo has no financial relationships to disclose or Conflicts of Interest to resolve. Any real or apparent conflicts of interest related to the content of this presentation have been resolved.

- This presentation will not involve discussion of unapproved or off-label, experimental or investigational use of a drug.

Background

- Awaiting resolution of apnea of prematurity may prolong hospitalization in moderately preterm infants.
- A survey of physicians showed that 64%, 40%, and 34% of physicians in the US, Canada, and France, respectively, commonly use home caffeine therapy in preterm infants (Carlos C et al, J Neonatal Perinatal Med. 2015).
- In a cohort of over 5,000 preterm infants in Canada, 36% of preterm infants were discharged home on caffeine (Lodha et al, JAMA Peds, 2015).
- However, there are limited high-level of evidence data to support the use of caffeine therapy following discharge.
- Thus, we evaluated if extending caffeine treatment reduces the duration of hospitalization.

Hypothesis

In moderately preterm infants with planned discontinuation of caffeine, continuing caffeine until 28 days after discharge home compared to placebo decreases the number of days of hospitalization.

Secondary Outcomes

Secondary outcomes included:

- Number of days to physiologic maturity (apnea-free, full oral feeds, open crib)
- PMA at discharge
- Number of all-cause readmissions to a hospital and all-cause sick visits to urgent care, emergency room, or health care provider's office within the first 8 weeks after discharge from the hospital

Study Design

Randomized placebo-controlled trial with parallel allocation conducted at the 15 NRN sites

Infants born from 29 weeks 0 days to 33 weeks 6 days of gestation were eligible for enrollment

Inclusion Criteria

- PMA of 33-0/7 – 35-6/7 weeks at the time of randomization
- Receiving caffeine with plan to discontinue treatment
- Receiving full volume feeding (defined by a volume of ≥120 ml/kg/day) by oral and/or tube

Exclusion Criteria

- On respiratory support
- Plans to be discharged home on apnea monitor
- Parental request for apnea monitor
- Congenital heart disease other than ASD, VSD, or PDA
- Neuromuscular condition affecting respiration
- Major congenital malformation and/or genetic disorder
- Plans to transfer to a non-NRN site before discharge

Intervention

Infants were randomized to:

Intervention: continuing enteral caffeine at a dose of 10 mg/kg/day (5 mg/kg caffeine base) or

Control: an equal volume of placebo

given daily, continuing during the hospital stay and for 28 days after hospital discharge (28 numbered vials oral caffeine citrate or placebo).

Adverse and Safety Outcomes

Serious adverse events included:

- Arrhythmias (excluding those due to tachycardia or bradycardia)
- Seizures
- Hospitalization and sick visit related to apneic or apparent life-threatening events

Other safety/adverse outcomes

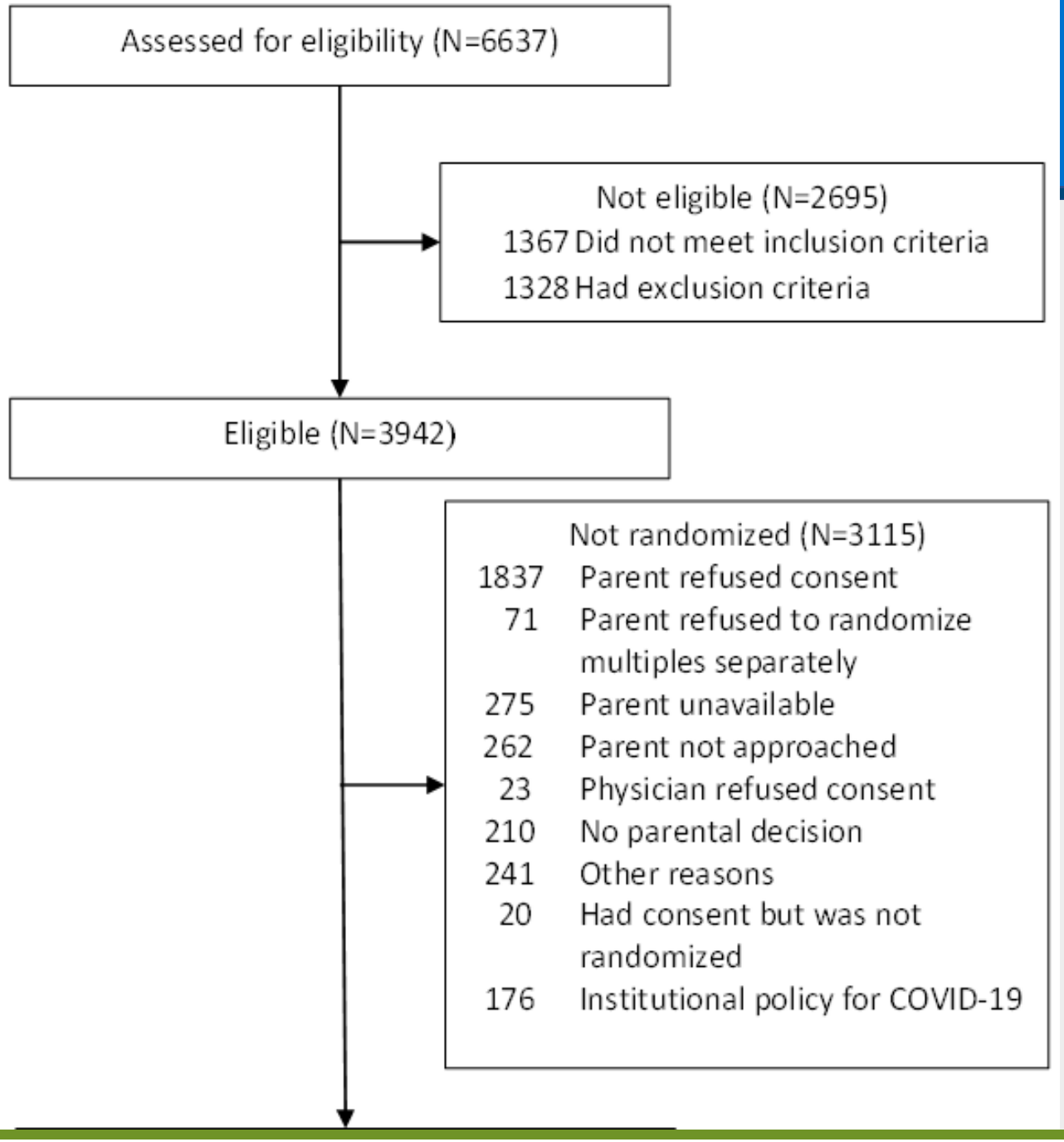
Statistical Considerations

To detect a two-day difference in primary outcome of days from randomization to discharge, from 14 days to 12 days, with 80% power, significance of 0.05, and 5% attrition, the trial required 439 infants per groups (intervention and placebo) for a total of 878 infants, assuming a two-tailed non-parametric test comparing median length of stay after randomization between groups.

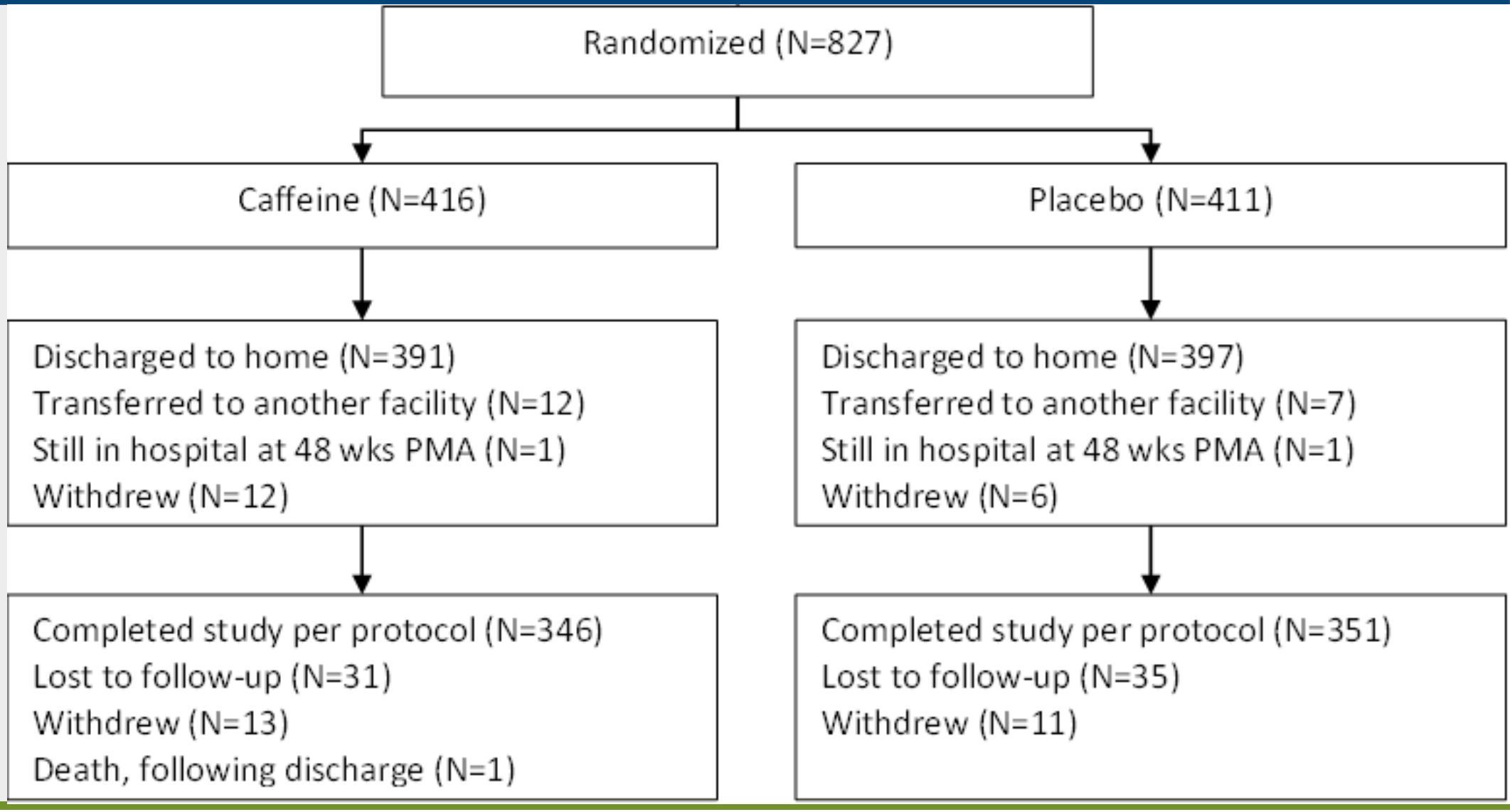
Results

Enrollment was stopped early when 827 of the planned 878 infants had been randomized (416 caffeine, 411 placebo) upon recommendation of the DSMC because of reaching a pre-specified futility threshold.

Consort


Assessed for eligibility (N=6637)
Not eligible (N=2695)
1367 Did not meet inclusion criteria
1328 Had exclusion criteria
Eligible (N=3942)
Not randomized (N=3115)
1837 Parent refused consent
71 Parent refused to randomize multiples separately
275 Parent unavailable
262 Parent not approached
23 Physician refused consent
210 No parental decision
241 Other reasons
20 Had consent but was not randomized
176 Institutional policy for COVID-19

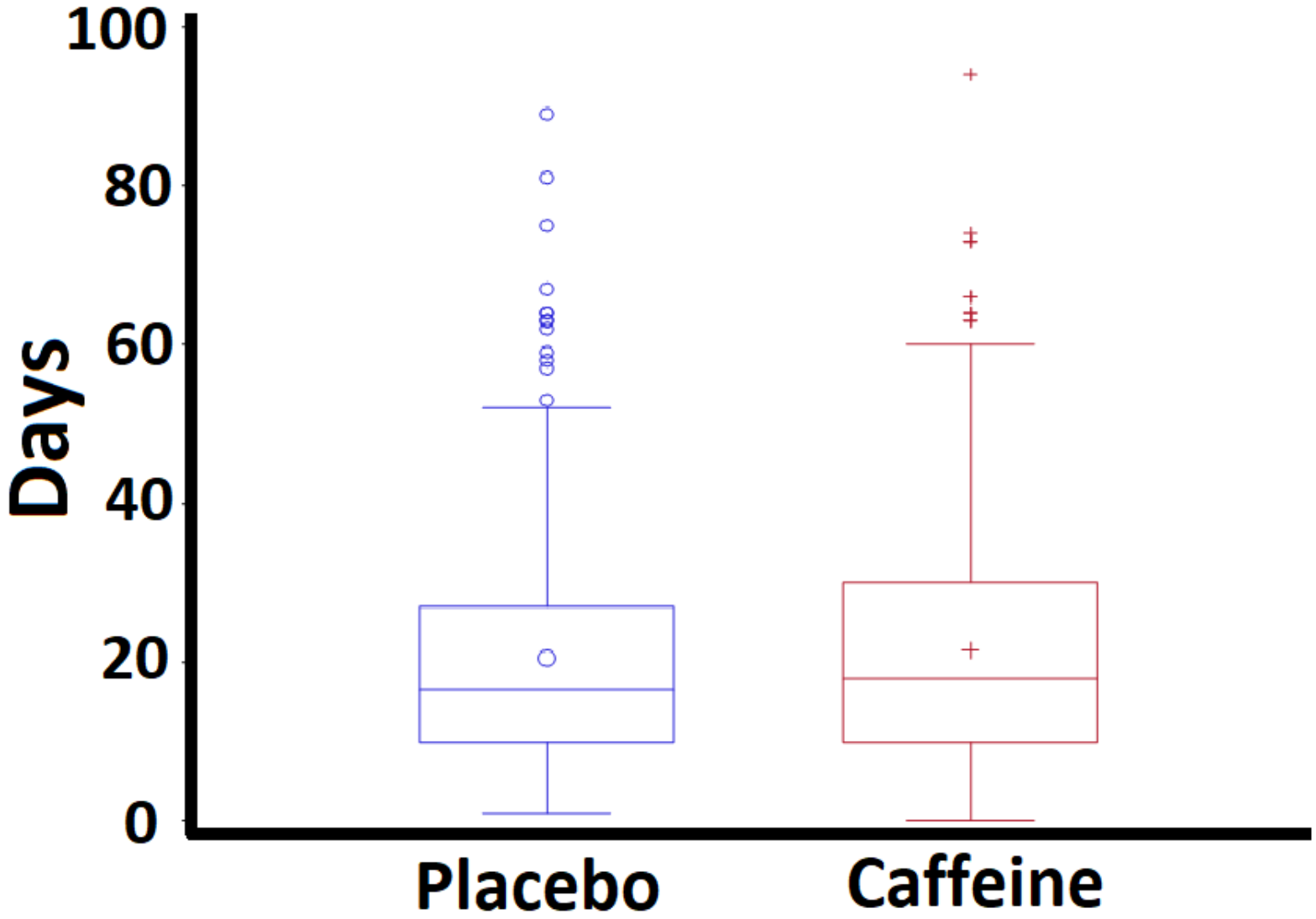
Consort


Randomized (N=827)
Caffeine (N=416)
Placebo (N=411)
Discharged to home (N=391)
Transferred to another facility (N=12)
Still in hospital at 48 wks PMA (N=1)
Withdrew (N=12)
Discharged to home (N=397)
Transferred to another facility (N=7)
Still in hospital at 48 wks PMA (N=1)
Withdrew (N=6)
Completed study per protocol (N=346)
Lost to follow-up (N=31)
Withdrew (N=13)
Death, following discharge (N=1)
Completed study per protocol (N=351)
Lost to follow-up (N=35)
Withdrew (N=11)

Demographics and Baseline Characteristics

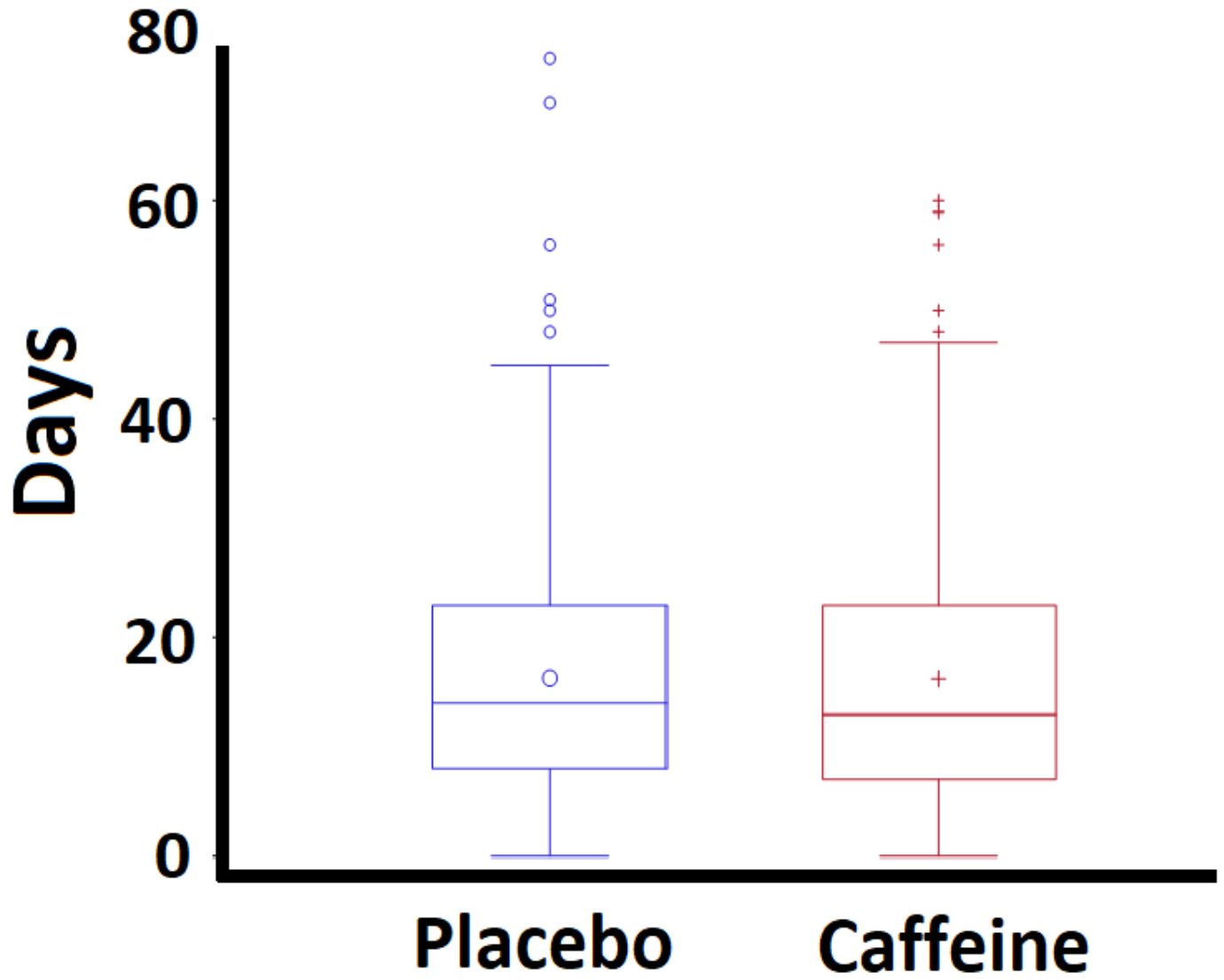
Characteristic	Caffeine (N=416)	Placebo (N=411)
Gestational age, weeks, mean(SD)	31.2 (1.2)	31.2 (1.2)
Birth weight, g, mean (SD)	1545 (358.1)	1564 (357.4)
PMA at enrollment, wks, mean (SD)	34.7 (0.8)	34.7 (1.0)

Days of Hospitalization



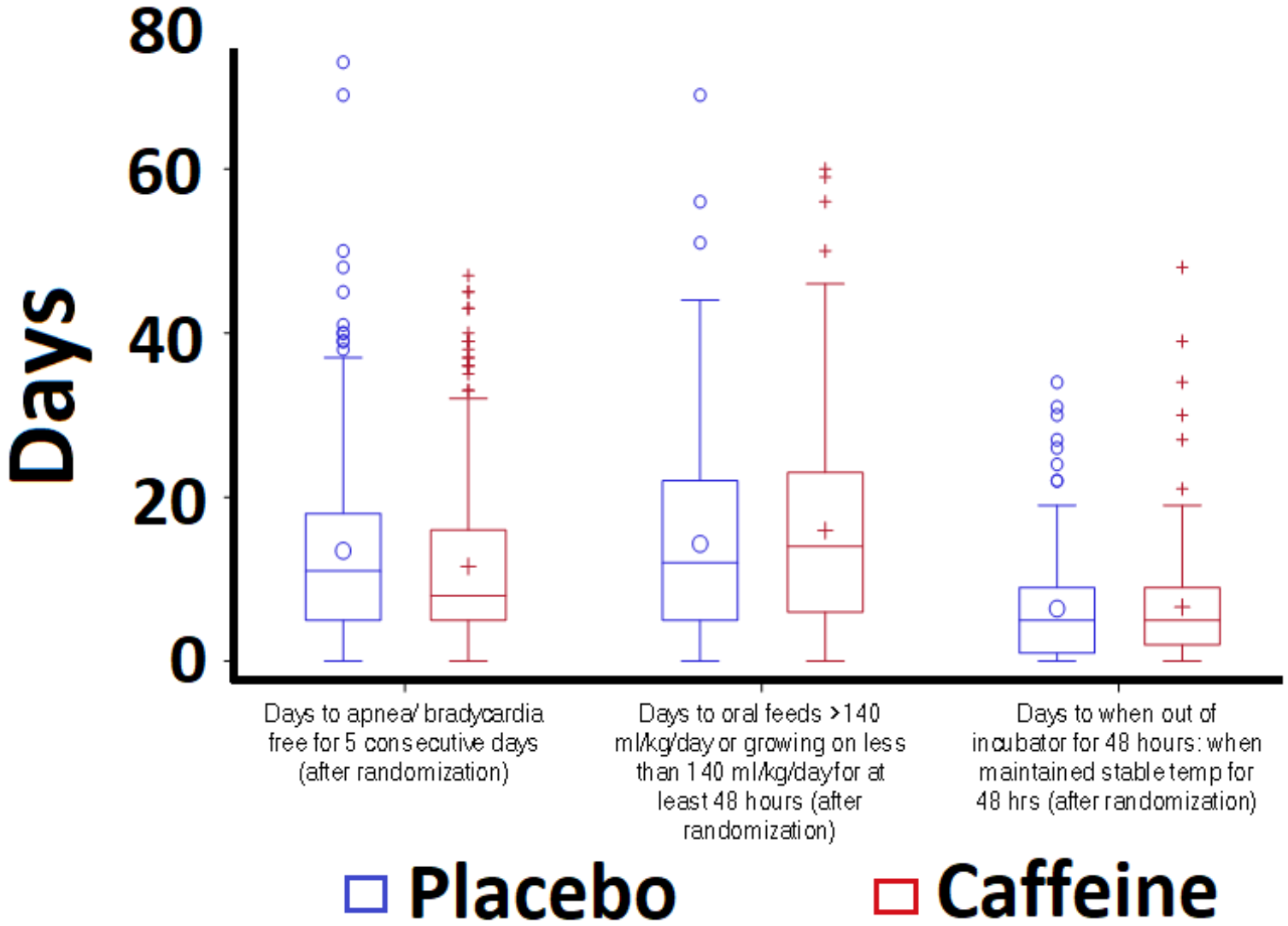
The number of days of hospitalization from randomization to discharge did not differ between the caffeine and the placebo groups (adjusted difference in medians 0, IQR (-1.6, 1.6), p>0.99).

Days to Physiologic Maturity



The number of days to physiologic maturity did not differ between groups (difference in medians 0 days, with IQR -1.6, 1.6).

Days to Components of Physiologic Maturity



- The number of days to AoP-free sooner (adjusted difference in median days was) -2.0, with interquartile range -3.3, -0.7.
- The number of days to attainment of oral feeds ≥140 ml/kg/day or growing on less than 140 ml/kg/day for at least 48 hours did not differ between the groups.
- The number of days when out of incubator for 48 hours did not differ between the groups.

Other Secondary Outcomes

Characteristic	Caffeine (N=416)	Placebo (N=411)	Model-estimated Difference in Relative Risk (95% CI)
Significant apnea/ bradycardia n/N (%)	4/414 (1.0)	18/410 (4.4)	0.22 (0.07, 0.65)
All-cause mortality n/N (%)	1/416 (0.2)	0/411 (0.0)	_
NPO for >24 hours n/N (%)	6/414 (1.4)	14/411 (3.4)	0.42 (0.16, 1.08)
Anti-reflux medications n/N (%)	30/414 (7.2)	24/411 (5.8)	1.25 (0.73, 2.1)

Other Secondary Outcomes

Characteristic	Caffeine (N=416)	Placebo (N=411)	Model-estimated Difference in Relative Risk (95% CI)
Weight change, g/day, mean, SD	28.9 (8.7)	32.2 (12.8)	-3 (-5, -2)
Weight at status, g, mean (SD)	2856 (545)	2659 (602)	-74 (-148, 0)
HR >200, n/N (%)	35/414 (8.5)	15/411 (3.6)	2.43 (1.34, 4.25)
Hypertension, n/N (%)	2/414 (0.5)	1/411 (0.2)	2.2 (0.19, 24.4)

Summary of Post-discharge Outcomes

Post-discharge Outcome	Caffeine (N=393) Evt/Subj(%)	Placebo (N=411) Evt/Subj(%)	Relative Risk (95% CI)
Any all-cause readmissions	27/24 (6)	30/25 (6)	0.97 (0.56, 1.65)
Any all-cause sick visits, urgent care, emergency rooms, or health care provider's office	126/89 (23)	106/77 (19)	1.17 (0.91, 1.47)
Any sick visits related to apneic or apparent life-threatening events	31/22 (6)	35/29 (7)	0.77 (0.45, 1.31)

Conclusions

In moderately preterm infants with planned discontinuation of caffeine, continuing caffeine until 28 days after discharge home does not reduce hospitalization days, hospital readmissions, or sick visits despite

- a reduction in the number of apnea/bradycardia-free days from 11 to 8 and
- a reduction in the proportion of infants with significant apnea post randomization from 4.4% to 1.0%.

Achievement of full oral feeds delayed discharge more than apnea resolution (14 versus 8 days in the caffeine group).

Caffeine treatment could be tested in infants who have already achieved oral feeds before caffeine discontinuation but continue to have apnea.

Neonatal Research Network Centers (2016-2023)

- Brown University
- Case Western Reserve University
- Cincinnati Children's Medical Center
- Duke University
- Emory University
- Nationwide Children's Hospital, Ohio State University
- RTI International
- Stanford University
- University of Alabama at Birmingham
- University of Iowa
- University of New Mexico
- University of Pennsylvania
- University of Rochester
- University of Texas Southwestern
- University of Texas Health Science Center at Houston
- University of Utah