NICHD
NEONATAL RESEARCH NETWORK

Red Blood Cell Transfusions and Risk of Necrotizing Enterocolitis: A Hazard Period Analysis of the TOP Trial

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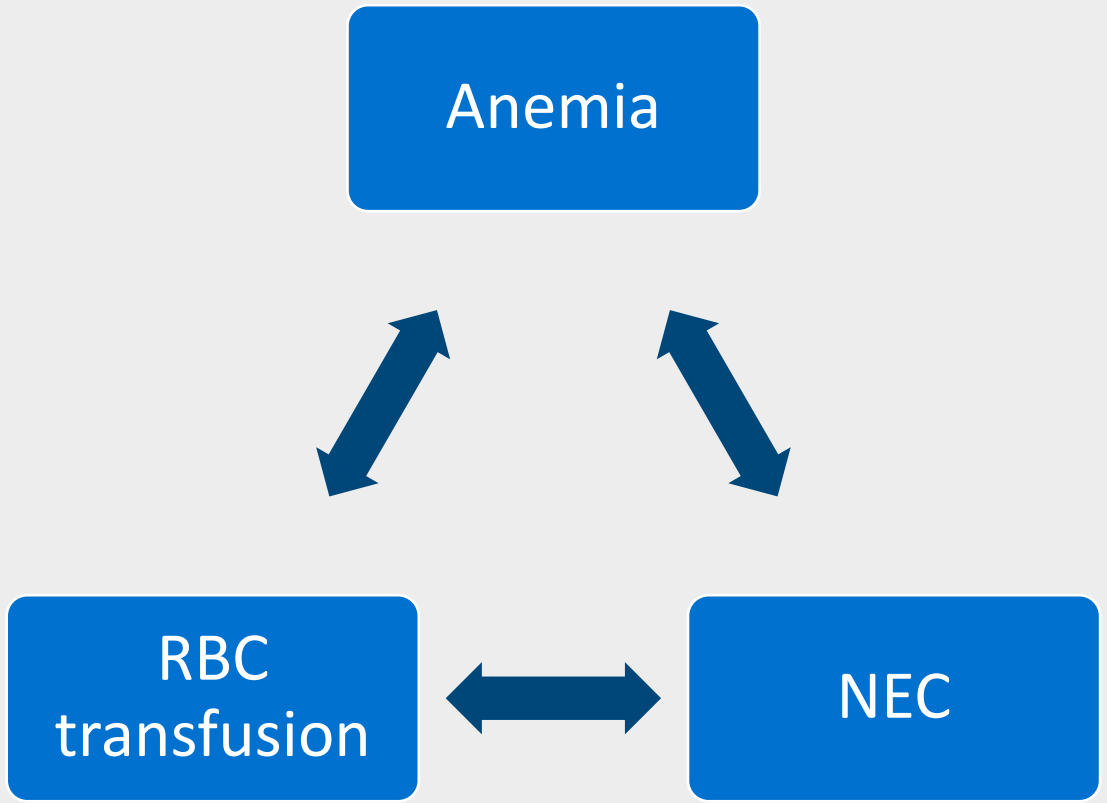
Disclosures

- Speaker: ARIEL A. SALAS

- Dr. SALAS has received honoraria from the Lockwood Group LLC for participation in advisory board meetings and submitted a U.S. patent application for an instrumented feeding bottle. 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.

Establishing a cause-effect relationship between RBC transfusions and NEC is difficult



OBSERVATIONAL DATA

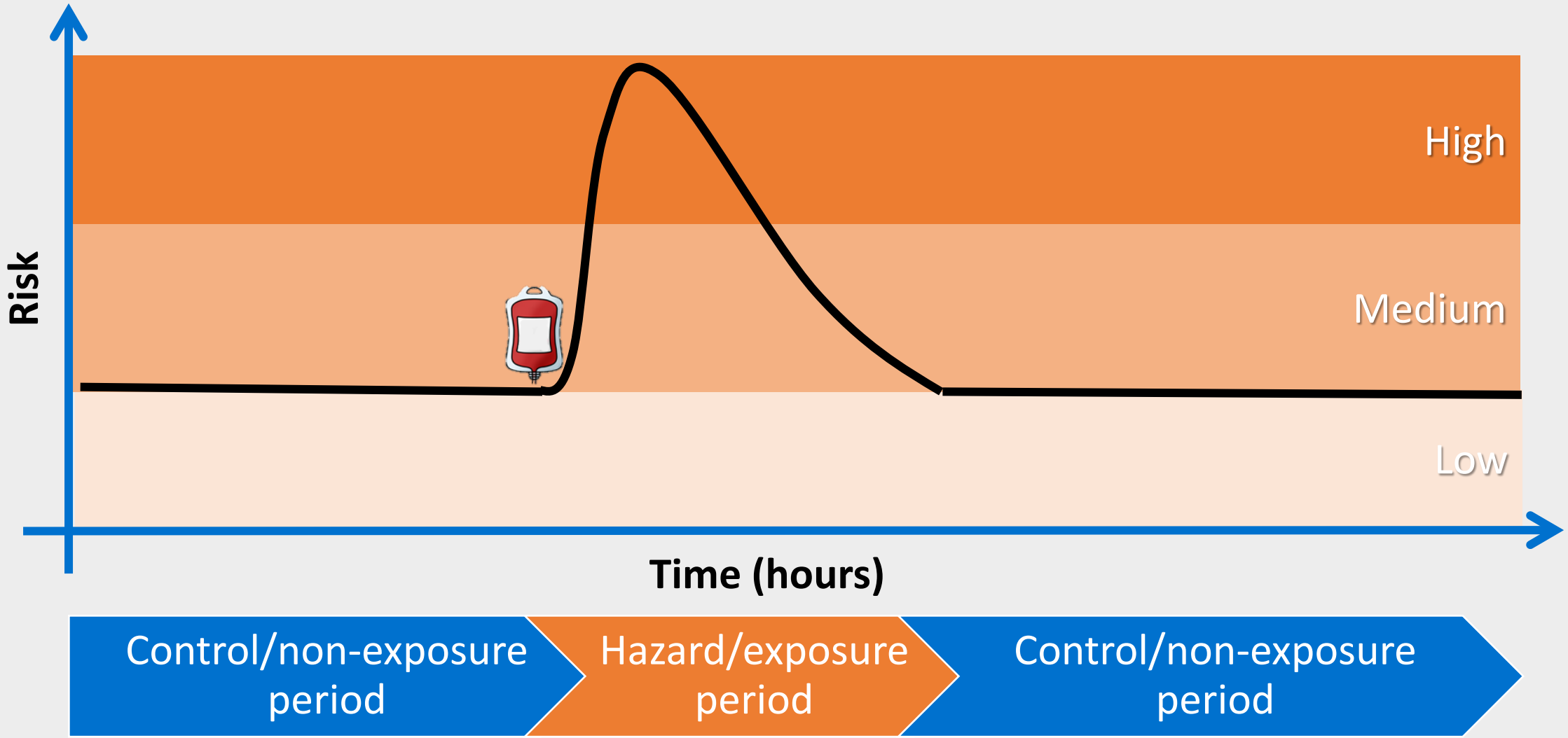
- Conflicting results suggest that RBC transfusions and severe anemia are associated with a higher risk of NEC

INTERVENTIONAL DATA (TOP & ETTNO)

- More PRBC transfusions and higher hemoglobin values (~1.5 g/dL higher) did not increase the risk of NEC in ELBW infants

Traditional study designs may be inadequate to mitigate confounding

Intermittent exposures to RBC transfusions have potentially short induction times and acute effects



Estimating individual risks under either exposure or non-exposure status could prove temporality

OBJECTIVE

- To quantify NEC events that occurred:
  - during hazard periods (defined by exposure to RBC transfusion)
  - during control unexposed periods

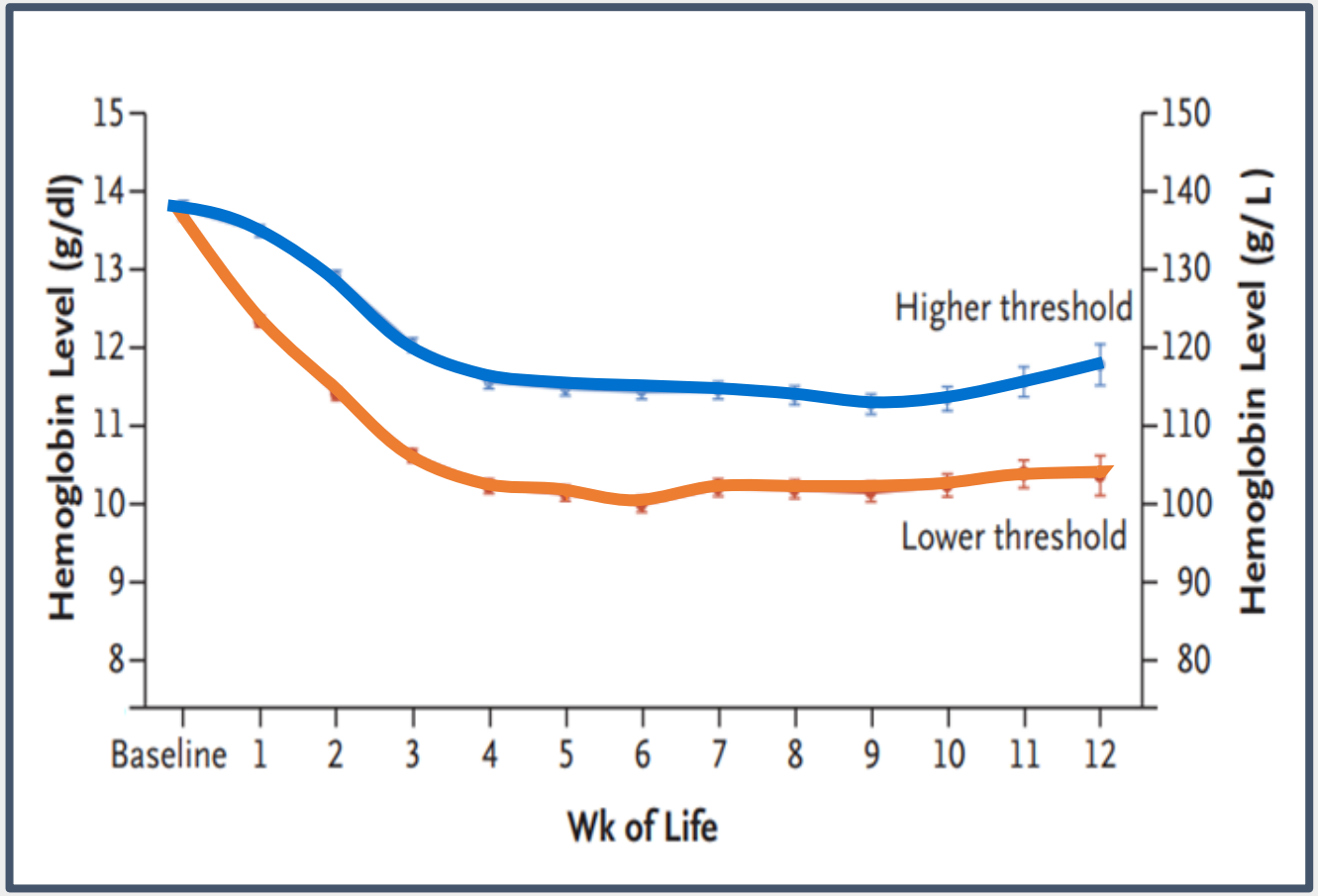
HYPOTHESIS

- The risk of NEC during hazard periods is not significantly higher than the risk of NEC during control periods in ELBW infants

Methods

STUDY DESIGN

- Secondary analysis of the TOP trial
  - Infants 22 to 28 weeks of gestation with BW < 1000g
  - 19 NRN centers
  - 2012 – 2017
- Selection criteria:
  - Survived to postnatal day 10
  - Did not develop SIP or NEC before postnatal day 10

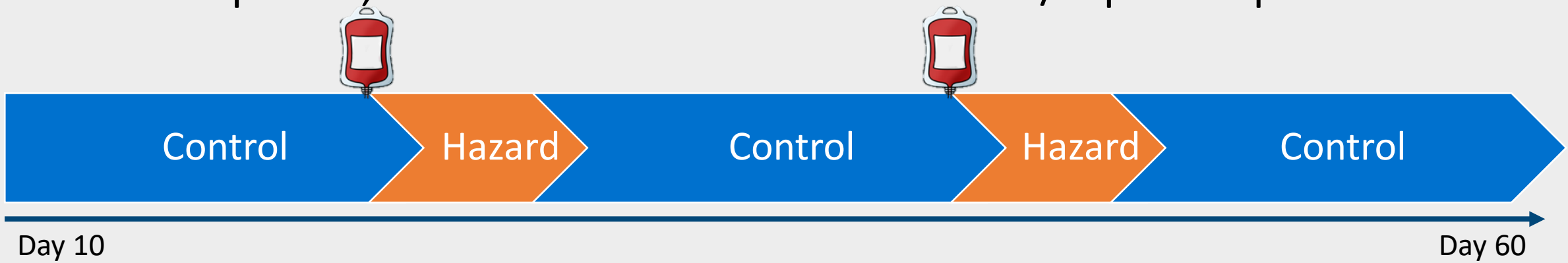


Kirpalani, et al, NEJM 2020

Methods

AT-RISK OF NEC FOLLOW-UP PERIOD

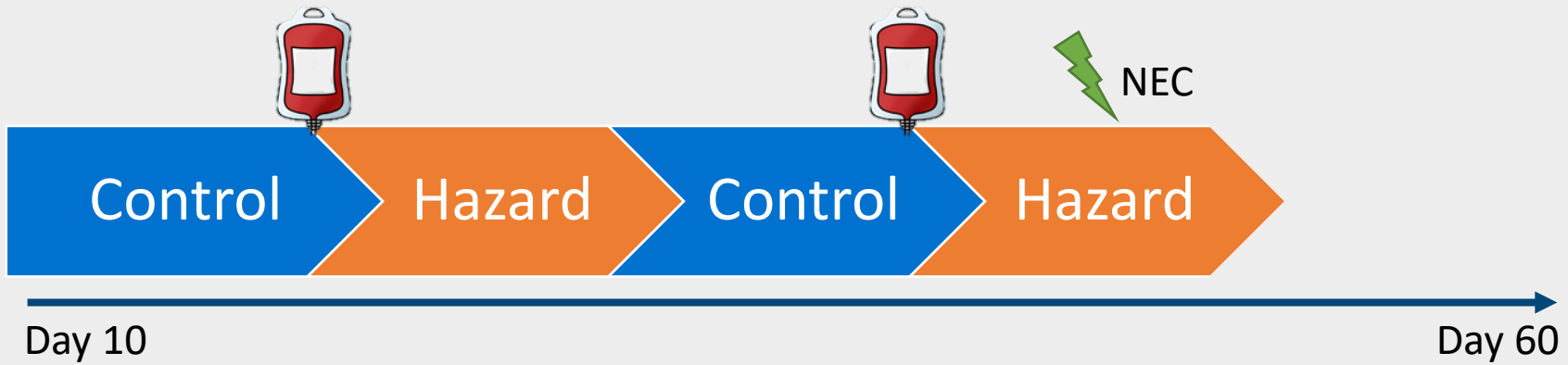
- Began on day 10 and ended on day 60 or on the day of diagnosis of NEC (whichever occurred earlier)
- After counting the number of RBC transfusions that occurred during the at-risk period, we determined individual hazard/exposure periods



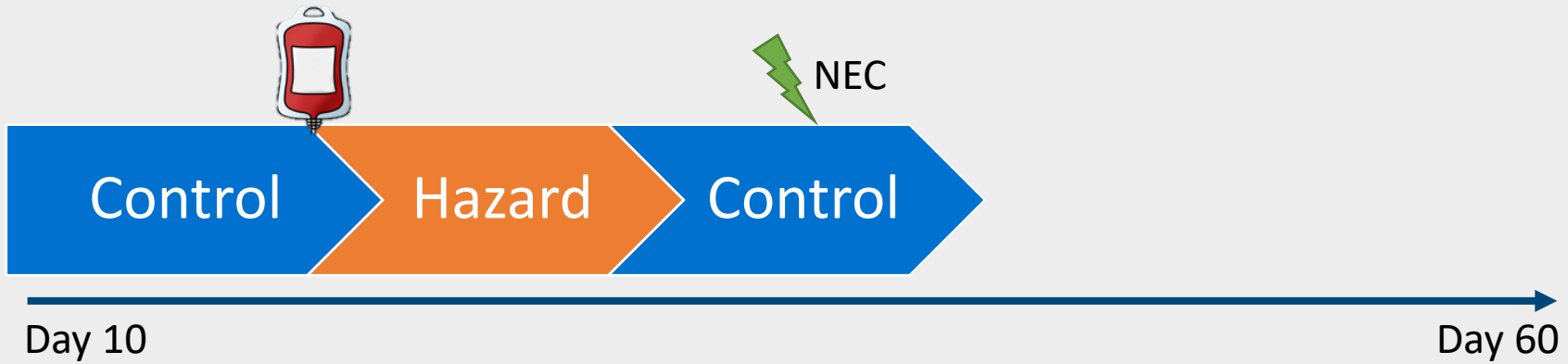
- A hazard (exposure period) began on the hour of the transfusion and ended 72 hours later (fixed duration).

Methods

- Unadjusted comparison of:
  - NEC events that occurred during any hazard period



  - NEC events that occurred during any control period

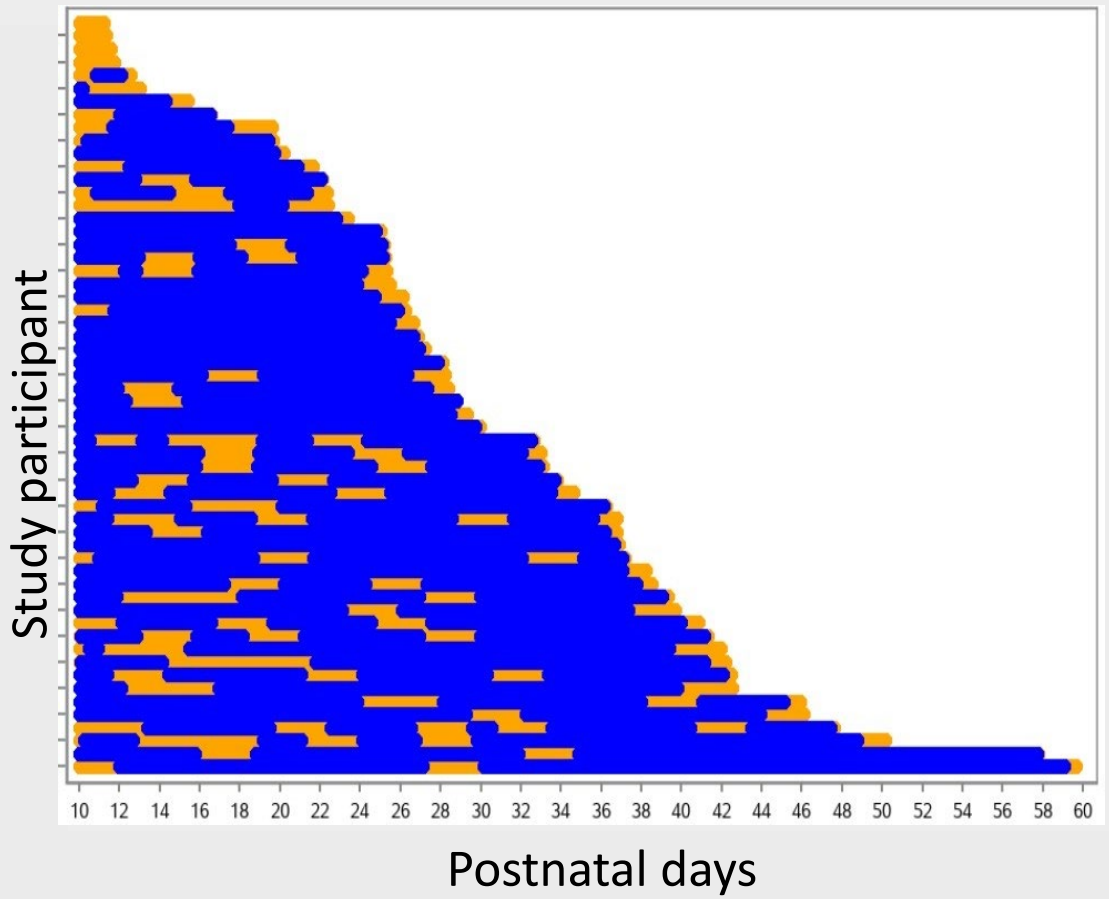


Results

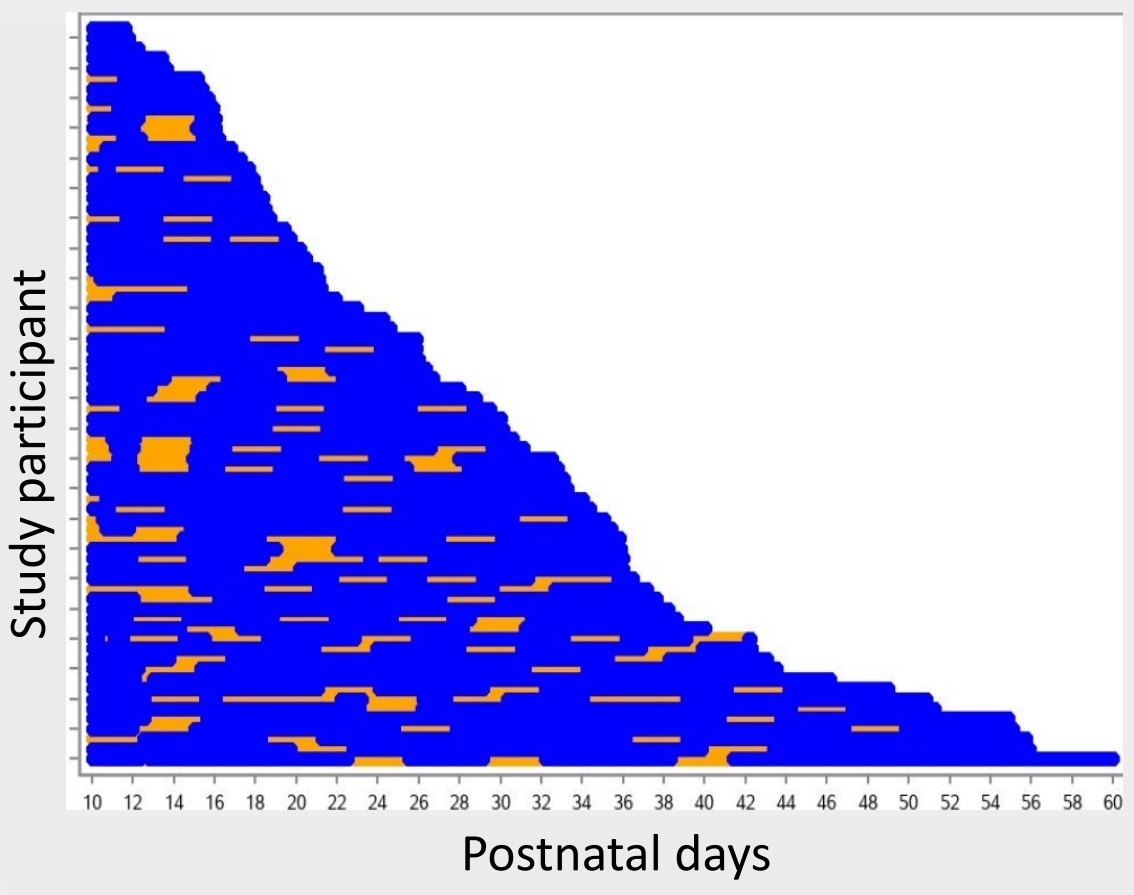
- 1653 ELBW infants were considered at risk of NEC after postnatal 10:
  - 4885 hazard periods and 5709 control periods
  - 133 infants developed NEC stage 2 or greater (8%)
    - 59 NEC events occurred during hazard periods
    - 74 NEC events occurred during control periods
- The frequency of NEC was 12 per 1000 hazard periods and 13 per 1000 control periods (p=0.73)

NEC cases according to hazard and control periods

NEC CASES DURING HAZARD PERIODS (n=59)



NEC CASES DURING CONTROL PERIODS (n=74)



Post-transfusion hazard periods Control periods

Results: NEC cases during hazard and control periods

Characteristic	NEC during hazard periods (n=59)	NEC during control periods (n=74)
Maternal age, yr	28±6	27±6
Black race, %	60	49
Private insurance, %	22	22
Multiple gestation, %	15	24
Hypertension, %	22	36
ANS exposure, %	93	89
Birth weight, kg	0.75±0.14	0.74±0.14
Gestational age, wk	25.6 ±1.2	26.0±1.7
Female, %	48	60
Age BW was first regained, wk	2±1	2±1
Age at first enteral feed, d	4±2	5±7
Age at full enteral feeding, d	26±19	25±17
Breast milk use in the first month, d	18±8	17±6
RBC transfusions before PD 10	1.7±1.4	1.5±1.4

Results

		NEC events		NEC rate	Risk ratio estimate
		Yes	No		
High threshold group (Higher hemoglobin)	Hazard periods	29	2826	10.2 per 1000 transfusion periods	0.70 (95% CI: 0.43 – 1.13)
	Control periods	36	3185	11.2 per 1000 control periods	
Low threshold group (Lower hemoglobin)	Hazard periods	30	2059	14.4 per 1000 transfusion periods	0.98 (95% CI: 0.61 – 1.57)
	Control periods	38	2524	14.8 per 1000 control periods	

Strengths

- Our study design with individual risk analyses
  - Accounts for temporality
  - Makes adjusted analyses less critical
  - Estimates the baseline risk of NEC before any RBC transfusion
- Our approach to select infants at risk of NEC
  - Lessens the impact of acute critical illness
  - Excludes SIP cases
- Our stratified analysis according to randomization groups
  - Minimizes the confounding effect of anemia

Study design limitations

- Assumes a similar baseline risk of NEC
- Assumes transient effects of RBC transfusions on NEC
- Anticipates a 2% difference between groups
  - Insufficient power to detect smaller differences
- Employs an arbitrary definition of 72-h hazard periods
  - Sensitivity analyses were not performed
- Disregards variability in the duration of control periods
  - Risk estimates were not adjusted

Conclusion

- In ELBW infants with hemoglobin transfusion thresholds defined by the TOP trial, RBC transfusions are not associated with a higher risk of NEC.
- These results support the finding of the TOP trial that higher hemoglobin thresholds for RBC transfusion do not increase the risk of NEC.

Neonatal Research Network Centers (2012-2017)

- Brown University
- Case Western Reserve University
- Children's Mercy Hospitals and Clinics, University of Missouri-Kansas City
- Cincinnati Children's Medical Center
- Duke University
- Emory University
- Indiana University
- Nationwide Children's Hospital, Ohio State University
- RTI International
- Stanford University
- University of Alabama at Birmingham
- University of California – Los Angeles
- 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
- Wayne State University