Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Kirpalani H, Bell EF, Hintz SR, et al. Higher or lower hemoglobin transfusion thresholds for preterm infants. N Engl J Med 2020;383:2639-51. DOI: 10.1056/NEJMoa2020248

List of Supplemental Tables

Table S1. Investigators, Sites and Sponsors

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The following authors have made significant contributions as determined by the Uniform Requirements for Manuscripts Submitted to Biomedical Journals:

- Haresh Kirpalani, MB MSc, is the co-lead principal investigator (PI) for the TOP trial, the Chair of the TOP Protocol Subcommittee, and Co-PI for the University of Pennsylvania. He developed the trial, monitor trial implementation and follow-up, and drafted the manuscript. As the co-PI at the University of Pennsylvania, he oversaw recruitment at the site – which enrolled 190 infants into this trial. Dr. Kirpalani drafted the manuscript, chaired the writing committee, and received input from the authors below as part of manuscript revision.

- Edward F. Bell, MD, is the co-lead principal investigator (PI) for the TOP trial, the Co-Chair of the TOP Protocol Subcommittee, and the PI for the University of Iowa, which recruited 133 infants into the trial. He helped developed the trial and monitored implementation. He was a member of the writing committee, contributed critical revisions of the manuscript and approved the final manuscript for submission.

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- Sylvia Tan, MS, served as the primary statistician for the trial, providing statistical input for protocol development and completing the statistical analyses for the paper. She developed the tables for the paper, was a member of the writing committee, and provided critical revision to the manuscript and approved the final version of the manuscript.

- Barbara Schmidt, MD MSc, is a member of the TOP Subcommittee and was the PI for the University of Pennsylvania, which recruited 190 infants for the trial. She was a member of the writing committee, contributed critical revisions of the manuscript and approved the final manuscript for submission.

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- Abhik Das, PhD, is the PI for the NRN Data Coordinating Center and a member of the TOP Protocol Subcommittee. Dr. Das oversaw all aspects of the statistical analysis, was a member of the writing committee, provided critical revisions to the manuscript and approved the final version of the manuscript.

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Table S2. Intervention Algorithm, Hemoglobin[a] RBC Transfusion Thresholds in g/dL by Postnatal Age and Received Respiratory Support

	High hemoglobin threshold		Low hemoglobin threshold	
	Respiratory support[b]	**No respiratory support**	**Respiratory support**	**No respiratory support**
Post-natal Age				
Week 1	13.0	12.0	11.0	10.0
Week 2	12.5	11.0	10.0	8.5
Weeks ≥3	11.0	10.0	8.5	7.0

[a] This table was also provided as hematocrit, using the conversion formula: Hematocrit (%) = 2.941 x Hgb (g/dl) (http://www.heartpumper.com/hematocrit.htm).

[b] Respiratory support was defined as mechanical ventilation, continuous positive airway pressure, F_iO_2 >0.35, or nasal cannula ≥1 liter per min (room air nasal cannula ≥1 liter per min was considered respiratory support).

Table S3. List of all Pre-specified Secondary Outcomes

Short term, to NICU discharge:

(a) Survival to discharge without severe morbidity, defined as any of the following: bronchopulmonary dysplasia, retinopathy of prematurity (stage >3 or requiring treatment), or serious brain abnormality (grade 3 or 4 intraventricular hemorrhage, periventricular leukomalacia, or ventriculomegaly).

(b) Weight, length, and head circumference at 36 weeks postmenstrual age or at discharge from NICU, whichever occurs first

(c) Serious abnormality on cranial ultrasound examination: grade 3 or 4 intraventricular hemorrhage, periventricular leukomalacia, or ventriculomegaly;

(d) Age at final tracheal extubation; age at final caffeine dose

(e) Number of transfusions, numbers of donor exposures by RBC donors or other blood product

(g) For survivors, length of hospital stay in the level 3 NICU referral site, or in the level 3 area of the referral site;

(h) Episodes of necrotizing enterocolitis of Bell stage 2 or higher, and time to full feeds;

Long term (survivors only), at 22–26 months corrected age:

(i) The incidence of ambulatory and non-ambulatory CP defined by GMFCS;

(j) Hydrocephalus shunt, microcephaly, or seizure disorder;

(k) The presence of respiratory disease necessitating readmission before 22–26 months follow-up.

(l) All individual components of the composite outcome of NDI or death, including cognitive outcomes at follow-up at 1 SD cut-off on the BSID III standardized scales

(m) BSID III cognitive, language and motor scores at 2 SD cut-offs (<70) at follow-up.

(n) Economic cost-benefit analysis to time of discharge and to 22–26 month follow-up.

Table S4. Additional Infant Characteristics

Characteristic		Analysis Cohort[a] High Hemoglobin Threshold (N=845)	Analysis Cohort[a] Low Hemoglobin Threshold (N=847)	All Randomized High (N=911)	All Randomized Low (N=913)
	n / N (%) subjects, unless otherwise noted.				
Neonatal Characteristics					
Birth weight stratum at randomization	<750 g	391/845 (46%)	387/847 (46%)	421/911 (46%)	417/913 (46%)
	750-1000g	454/845 (54%)	460/847 (54%)	490/911 (54%)	496/913 (54%)
Full course of antenatal steroids given		569/844 (67%)	565/846 (67%)	607/910 (67%)	610/909 (67%)
Intubation at randomization		574/845 (68%)	524/847 (62%)	612/911 (67%)	560/913 (61%)
SNAP-II[b] score at randomization	Mean (SD)	23.1 (14.6)	23.4 (14.4)	22.8 (14.6)	23.3 (14.4)

Characteristic		Analysis Cohort[a] High Hemoglobin Threshold (N=845)	Analysis Cohort[a] Low Hemoglobin Threshold (N=847)	All Randomized High (N=911)	All Randomized Low (N=913)
	n / N (%) subjects, unless otherwise noted.				
SNAPPE-II[c] score at randomization	Mean (SD)	46.2 (20.8)	46.1 (20.4)	45.7 (20.8)	46.0 (20.2)
SGA[d]		96/845 (11%)	80/847 (9%)	108/911 (12%)	85/913 (9%)
Corrected age at follow-up exam (mo)	Mean (SD)	24.4 (2.7)	24.6 (2.7)	n/a	n/a

[a] The Analysis Cohort includes subjects with complete data for the primary outcome.

[b] SNAP-II (Score for Neonatal Acute Physiology II - See Zupancic JA, Richardson DK, Horbar JD, Carpenter JH, Lee SK, Escobar GJ. Revalidation of the Score for Neonatal Acute Physiology in the Vermont Oxford Network. Pediatrics. 2007;119(1):e156-63) is missing for 5% of subjects in the High and for 6% in the Low threshold group. Higher scores indicate greater severity of illness.

[c] SNAPPE-II (Score for Neonatal Acute Physiology with Perinatal Extension II - Zupancic JA, Richardson DK, Horbar JD, Carpenter JH, Lee SK, Escobar GJ. Revalidation of the Score for Neonatal Acute Physiology in the Vermont Oxford Network. Pediatrics. 2007;119(1):e156-63.) is missing for 5% of subjects in the High and for 7% in the Low threshold group. Higher scores indicate greater severity of illness.

[d] Small for gestational age (SGA) was defined as weight <10th percentile according to the Alexander growth curve (Alexander GR, Himes JH, Kaufman RB, Mor J, Kogan M. A United States national reference for fetal growth. *Obstet Gynecol*. 1996; 87:163-168)

Table S5. Violations of Transfusion Algorithms

	High Hemoglobin Threshold	Low Hemoglobin Threshold	Total	Adjusted[a] Odds Ratio / Mean Difference (95% CI)
Transfusion Characteristics				
Total number of transfusions	5624	4055	9679	
a) Number of protocol compliant transfusions	5342 (95%)	3115 (77%)	8457 (87%)	Reference
b) Number of clinically justified non-protocol transfusions	238 (4%)	641 (16%)	879 (9%)	0.22 (0.18, 0.25)[b]
c) Number of unjustified non-protocol transfusions (violations)[c]	44 (0.8%)	299 (7.4%)	343 (3.5%)	0.09 (0.06, 0.12)[b]

	High Hemoglobin Threshold	Low Hemoglobin Threshold	Total	Adjusted[a] Odds Ratio / Mean Difference (95% CI)
Reason for clinically justified non-protocol transfusions:				
i) Bleeding	18 (7.6%)	62 (9.7%)	80 (9.1%)	
ii) Surgery	68 (28.6%)	127 (19.8%)	195 (22.2%)	
iii) Sepsis-shock	40 (16.8%)	99 (15.4%)	139 (15.8%)	
iv) Severe hypotension	44 (18.5%)	141 (22.0%)	185 (21.0%)	
v) Severe hypoxemia	60 (25.2%)	189 (29.5%)	249 (28.3%)	
vi) Other reason	8 (3.4%)	23 (3.6%)	31 (3.5%)	
Transfusions that were missed[d]				
Number of justified missed transfusions	76 (1.4%)	5 (0.2%)	81 (0.9%)	8.77 (3.54, 21.72)[e]
Number of missed transfusions (violations)	185 (3.3%)	33 (1.0%)	218 (2.5%)	3.19 (2.20, 4.63)[e]

	High Hemoglobin Threshold	Low Hemoglobin Threshold	Total	Adjusted[a] Odds Ratio / Mean Difference (95% CI)
Transfusion violations[f]				
Total number of transfusion violations	229	332	561	
Per subject number of transfusion violations (Mean {SD})	0.25 (0.66)	0.36 (0.85)	0.31 (0.77)	-0.12 (-0.18, -0.05)[g]

[a] Estimates are adjusted for birth weight and center stratum. Ninety-five percent confidence intervals are not adjusted for multiplicity; they should not be used to infer definitive treatment effects.

[b] Multinomial logistic regression estimating the joint adjusted odds of having a justified clinical transfusion or an unjustified transfusion versus a compliant one, for the High versus Low hemoglobin threshold group.

[c] Unjustified clinical reasons, classified as violations include: apnea and bradycardia / desaturation (n=54), tachycardia (n=18), error or misinterpretation of protocol (n=44), physician preference (n=90), respiratory requirements < 100% (n=61), non-severe sepsis (n=22), other reason such as acidosis or anemia (n=54).

[d] Missed transfusions are transfusions that should have taken place, per protocol, but were not performed. Justified missed transfusions are due to parental refusal (6%), lack of IV access (55%), or adjudicated clinical reason Patent Ductus Arteriosus, hyperbilirubinemia or fluid overload (29%). Percentages are out of all transfusions that should have taken place, calculated as adding both protocol compliant transfusions and missed transfusions; (for the high threshold group, n=5603; for the low threshold group, n=3153; total n=8756).

[e] Multinomial logistic regression estimating the joint adjusted odds of having a justified or an unjustified missed transfusion versus a compliant one, for the High versus Low threshold group.

[f] Adding both unjustified non-protocol transfusions and unjustified missed transfusions.

[g] Adjusted mean difference.

Table S6. Hemoglobin and Transfusion Outcomes

		High Hemoglobin Threshold	Low Hemoglobin Threshold	Adjusted mean difference[a] (95% CI)
Hemoglobin (g/dL)				
At Randomization	N[b]	911	912	
	Mean (SD)	13.8 (2.6)	13.7 (2.6)	0.06 (-0.17, 0.29)
Week 1	N	784	771	
	Mean (SD)	13.5 (1.5)	12.5 (1.8)	1.01 (0.86, 1.16)
Week 2	N	804	809	
	Mean (SD)	13.0 (1.4)	11.5 (1.4)	1.43 (1.31, 1.56)
Week 3	N	749	764	
	Mean (SD)	12.3 (1.4)	10.9 (1.5)	1.37 (1.24, 1.51)
Week 4	N	729	756	
	Mean (SD)	11.5 (1.3)	10.2 (1.3)	1.33 (1.20, 1.46)
	N	268	296	

		High Hemoglobin Threshold	Low Hemoglobin Threshold	Adjusted mean difference[a] (95% CI)
36 weeks PMA or discharge[c]	Mean (SD)	11.5 (1.6)	10.2 (1.4)	1.25 (0.99, 1.50)
Transfusions[d]				
Number of transfusions per subject				
– All	Mean (SD)	6.2 (4.3)	4.4 (4.0)	1.71 (1.37, 2.05)
– Triggered by hemoglobin	Mean (SD)	5.9 (4.0)	3.4 (3.0)	2.44 (2.15, 2.72)
– Clinical decision	Mean (SD)	0.3 (1.0)	1.0 (2.0)	-0.72 (-0.86, -0.58)
Number of RBC donor exposures per subject *	Mean (SD)	3.8 (2.8)	2.9 (2.4)	0.88 (0.66, 1.09)

[a] Estimates are adjusted for center and birthweight stratum. All are adjusted mean differences except where noted. Ninety-five percent confidence intervals are not adjusted for multiplicity; they should not be used to infer definitive treatment effects.

[b] The values of N vary, as there was no protocol-imposed hemoglobin testing schedule in place to guide transfusions.

[c] Closest Hgb measurement to 36 weeks postmenstrual age (PMA) or discharge, whichever is earlier.

[d] Reported for all randomized subjects (911 in High threshold group, 913 in Low threshold group).

* Post-hoc secondary outcome.

Table S7. Additional Secondary Outcomes at Discharge

Outcome		High Hemoglobin Threshold	Low Hemoglobin Threshold	
		n / N (%) subjects		*Adjusted[a] relative risk (95% CI)*
Death before 36 weeks PMA *		110/908 (12.1%)	101/906 (11.2%)	1.07 (0.84, 1.37)
Death before hospital discharge		127/908 (14.0%)	125/906 (13.8%)	1.00 (0.81, 1.25)
Patent ductus arteriosus *		404/907 (44.5%)	433/905 (47.8%)	0.93 (0.84, 1.02)
Early or late-onset sepsis *		227/889 (25.5%)	228/891 (25.6%)	0.99 (0.85, 1.16)
				Adjusted[a] hazard ratio (95% CI)
Time to regain birth weight (weeks)	N	887	887	1.08 (0.99, 1.19)[b]
	Mean (SD)	2.1 (1.1)	2.2 (1.2)	

Outcome		High Hemoglobin Threshold	Low Hemoglobin Threshold	
				Adjusted[a] mean difference (95% CI)
Length at 36 weeks' PMA (cm)				
	N	715	715	0.15 (-0.10, 0.41)
	Mean (SD)	42.1 (2.9)	42.0 (2.7)	
Weight at 36 weeks' PMA (g)	N	769	774	8.54 (-26.0, 43.0)
	Mean (SD)	2106 (398)	2098 (367)	
Head circumference at 36 weeks' PMA (cm)	N	754	766	-0.06 (-0.22, 0.10)
	Mean (SD)	30.4 (1.8)	30.4 (1.7)	

[a] Estimates are adjusted for birth weight and center stratum. For categorical outcomes, adjusted differences are adjusted relative risks, with the Low hemoglobin threshold group as reference. For time to regaining birth weight, they are adjusted hazard ratios with the Low hemoglobin threshold group as reference; for remaining continuous outcomes, they are adjusted mean differences. Ninety-five percent confidence intervals are not adjusted for multiplicity; they should not be used to infer definitive treatment effects.

[b] 887/906 (98%) in the High hemoglobin threshold group and 887/905 (98%) in the Low hemoglobin threshold group regained their birth weight during the period of observation. The hazard ratio, estimated via Cox proportional-hazards regression, may be interpreted as the odds of regaining birth weight faster at any point in time.

* Post-hoc secondary outcome.

Table S8. Additional Secondary Outcomes at 2 Years

Outcome		High Hemoglobin Threshold	Low Hemoglobin Threshold	
		n / N (%) subjects		*Adjusted[a] odds ratio (95% CI)*
CBCL Internalizing Problems Aggregate T-score[b]	>=64	78/685 (11.4%)	77/704 (10.9%)	1.04 (0.74, 1.47)
	60-63	63/685 (9.2%)	66/704 (9.4%)	0.97 (0.67, 1.41)
	<60	544/685 (79.4%)	561/704 (79.7%)	Ref[b]
CBCL Externalizing Problems Aggregate T-score[b]	>=64	86/685 (12.6%)	86/704 (12.2%)	1.03 (0.74, 1.42)
	60-63	56/685 (8.2%)	60/704 (8.5%)	0.95 (0.65, 1.41)
	<60	543/685 (79.3%)	558/704 (79.3%)	Ref[b]
CBCL Total Problems Aggregate T-score[b]	>=64	96/685 (14.0%)	92/704 (13.1%)	1.09 (0.80, 1.50)
	60-63	59/685 (8.6%)	54/704 (7.7%)	1.16 (0.78, 1.71)
	<60	530/685 (77.4%)	558/704 (79.3%)	Ref[b]

Outcome		High Hemoglobin Threshold	Low Hemoglobin Threshold	*Adjusted[a] mean difference (95% CI)*
BSID-III Cognitive Composite Score[c, *]	N	695	712	-0.11 (-1.61, 1.38)
	Mean (SD)	85.5 (15.0)	85.3 (14.8)	
BSID-III Language Composite Score[c, *]	N	671	691	-0.04 (-1.82, 1.73)
	Mean (SD)	81.8 (17.5)	81.5 (17.1)	
BSID-III Motor Composite Score[c, *]	N	678	695	0.37 (-1.24, 1.98)
	Mean (SD)	85.5 (15.9)	84.8 (15.8)	

[a] Estimates are adjusted for the birth weight and center stratum. For categorical outcomes, adjusted odds ratios are from a multinomial logistic regression, with the Low hemoglobin threshold group as reference. For continuous outcomes, they are adjusted mean differences. Ninety-five percent confidence intervals are not adjusted for multiplicity; they should not be used to infer definitive treatment effects.

[b] Child Behavior Checklist (CBCL) was rated as abnormal if Internalizing, Externalizing, and Total Problems aggregate T scores were ≥64 (clinical range); or borderline if 60-63. "Achenbach, T.M., & Rescorla, L.A. (2001). Manual for the ASEBA School-Age Forms & Profiles. Burlington, VT: University of Vermont, Research Center for Children, Youth, & Families". "Ref" denotes the reference level for statistical comparison, which is an aggregate T score <60.

[c] BSID III is the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley N. Bayley scales of infant and toddler development. 3rd ed. San Antonio, TX: Harcourt Assessments, 2006).

[*] Post-hoc outcome.

Table S9. Serious Adverse Event Reports

	High Hemoglobin Threshold (N=908)	Low Hemoglobin Threshold (N=906)
Any Serious Adverse Event (SAE)		
n (%) subjects	206 (22.7%)	197 (21.7%)
Adjusted[a] Relative Risk (95% C.I.)	1.04 (0.88, 1.23)	
Predefined SAEs, n (%) subjects[b]		
Respiratory deterioration[c]	93 (10.2%)	85 (9.4%)
Bell's stage > 2 NEC[d]	58 (6.4%)	62 (6.8%)
Spontaneous Intestinal Perforation	29 (3.2%)	38 (4.2%)
Nosocomial Sepsis[c]	31 (3.4%)	22 (2.4%)
Hyperkalemia – non-hemolyzed specimen[c]	10 (1.1%)	16 (1.8%)
Additional SAEs reported by sites, n (%) subjects[b]:		
Pulmonary hemorrhage	13 (1.4%)	9 (1.0%)
Severe hemorrhage	5 (0.6%)	2 (0.2%)

	High Hemoglobin Threshold (N=908)	Low Hemoglobin Threshold (N=906)
Renal failure	4 (0.4%)	2 (0.2%)
Pulmonary air leaks	1 (0.1%)	3 (0.3%)
Respiratory failure	0 (0.0%)	4 (0.4%)
Bowel obstruction	1 (0.1%)	2 (0.2%)
Persistent pulmonary hypertension	1 (0.1%)	2 (0.2%)
Seizures	2 (0.2%)	1 (0.1%)
Sepsis Bacterial	3 (0.3%)	0 (0.0%)
Sepsis Fungal	0 (0.0%)	3 (0.3%)
Adrenal insufficiency	2 (0.2%)	0 (0.0%)
Esophageal perforation	0 (0.0%)	2 (0.2%)
Pneumonia	1 (0.1%)	1 (0.1%)
Sepsis Viral	0 (0.0%)	2 (0.2%)
Severe hypotension	1 (0.1%)	1 (0.1%)

	High Hemoglobin Threshold (N=908)	Low Hemoglobin Threshold (N=906)
Thrombosis	1 (0.1%)	1 (0.1%)
Ascites	1 (0.1%)	0 (0.0%)
Hemolysis	1 (0.1%)	0 (0.0%)
Ischemic bowel	0 (0.0%)	1 (0.1%)
Severe cellulitis	1 (0.1%)	0 (0.0%)

[a] Relative risk is adjusted for birth weight and center stratum, and references the Low hemoglobin threshold group.

[b] In decreasing order of overall frequency

[c] Recorded in intake forms if event occurred up to 24 hours post-transfusion.

[d] Numbers differ from Table 3, as only subjects with SAEs are reported in this Supplemental Table. NEC denotes necrotizing enterocolitis.

Figure S1: Subgroup analysis by stratification variables: Sex, birth weight group and study center