

Transfusion of Prematures (TOP) Trial: Does a Liberal Red Blood Cell Transfusion Strategy Improve Neurologically-Intact Survival of Extremely-Low-Birth-Weight Infants as Compared to a Restrictive Strategy?

NICHD Neonatal Research Network

Manual of Operations

Version 1.8

Final: October 8, 2012
Revision: December 13, 2012
Revision: February 8, 2013
Revision: May 24, 2013
Revision: August 27, 2013
Revision: April 9, 2014
Revision: June 19, 2014
Revision: September 22, 2014
Revision: April 22, 2015

TABLE OF CONTENTS

CHAPTER 1. Study Overview	1-1
1.1 Introduction	1-1
1.2 Synopsis	1-1
1.3 Study Duration	1-2
1.4 Primary Outcome	1-2
1.5 Secondary Outcomes.....	1-2
1.6 Study Design.....	1-1
1.7 Inclusion Criteria	1-1
1.8 Exclusion Criteria	1-1
1.9 Center Baseline Information	1-1
1.10 Summary of Data Collection Forms.....	1-2
CHAPTER 2. Administration	2-1
2.1 Study Organization.....	2-1
2.2 The TOP Trial Subcommittee	2-1
2.3 Participating NICHD Neonatal Research Network Centers.....	2-1
2.4 Responsibilities of the Clinical Centers, the DCC and the NICHD	2-2
CHAPTER 3. Screening Log (TOP01)	3-1
3.1 Screening Log – Form TOP01.....	3-1
CHAPTER 4. Eligibility form (TOP02)	4-1
4.1 Eligibility Form TOP02.....	4-1
4.1.1 Section A. Inclusion Criteria	4-1
4.1.2 Section B. Exclusion Criteria	4-1
4.1.3 Section C. Consent	4-2
4.1.4 Section D. Randomization.....	~~4-14~~ 3
4.1.5 Section E. Data between birth and randomization	~~4-24~~ 4
CHAPTER 5. Randomization process	5-1
5.1 Randomization	5-1
5.2 Telephone Randomization System:.....	5-1
5.2.1 Calling the Randomization System.....	5-1
5.2.2 The Randomization Process	5-1
5.3 Randomization Tracking Tool.....	5-2
CHAPTER 6. SNAP SCORE FORM (TOP03)	6-1
6.1 SNAP Score Form (TOP03)	6-1
6.1.1 SNAP Measurements.....	6-1

CHAPTER 7. Transfusion triggers algorithms	7-1
7.1 Overview	7-1
7.2 High Threshold Algorithm	7-2
7.3 Low Threshold Algorithm	7-2
7.4 Ordering and Giving the Blood Transfusion	7-2
7.5 Time Interval Between Reaching the Trigger Threshold and Receipt of Blood	7-47-3
7.6 Volume of Transfusions and Hemoglobin Measures	7-47-3
7.7 Clinically Driven Transfusions or Algorithm Deviations	7-47-3
7.8 Maintaining Adherence to Algorithm and Minimizing Deviation from Protocol	7-57-4
7.9 Checking and Maintaining Compliance at the Bedside	7-57-4
7.10 Direct Donors	7-57-4
7.11 Transfusions and Blood Banking	7-57-4
 CHAPTER 8. HEMOGLOBIN/HEMATOCRIT Log (TOP04)	 8-1
8.1 Hemoglobin and Hematocrit Log Overview (TOP04)	8-1
8.1.1 Completing the Log	8-1
 CHAPTER 9. TransfusionS and Transfusion log (TOP05)	 9-1
9.1 Transfusion Overview	9-1
9.2 Transfusion Log (TOP05)	9-1
9.2.1 Section A: RBC Transfusion Record	9-1
9.2.2 Section B: Clinical Variables Prior, during and after the transfusion	9-2
 CHAPTER 10.GROWTH AND THERAPY FORM (TOP06)	 10-1
10.1 Growth and Therapy Form – TOP06	10-1
10.1.1 Section A: Growth Data	10-1
10.1.2 Section B: Therapy Data	10-1
 CHAPTER 11.Head Ultrasound form (top07)	 11-1
11.1 Head Ultrasound Form– TOP07	11-1
11.1.1 Section A. Pre-randomization HUS Results	11-1
 CHAPTER 12.In-Hospital Cost of Care Questionnaire (TOP08)	 12-1
12.1 In-Hospital Cost of Care Questionnaire – TOP08	12-1
12.1.1 Administering the questionnaire	12-1
12.1.1 Data entry	12-1
 CHAPTER 13.Adverse event form (TOP09)	 13-1
13.1 Adverse Event Form – TOP09	13-1
13.2 Instructions for Completing the Adverse Event Form	13-1
13.2.1 (1) Transfusion # from TOP05	13-1
13.2.2 (2) Adverse Event	13-1

13.2.3 (3) Onset Date,Time (4) Date Resolved	~~13-113-2~~
13.2.4 (5) Relationship	~~13-113-2~~
13.2.5 (6) Intensity Status	~~13-113-2~~
13.2.6 (7) Serious Status	~~13-213-3~~
13.2.7 (8) Expectations	~~13-213-3~~
13.2.8 (9) Actions Taken	~~13-213-3~~
13.2.9 (10) Final Outcome	13-3
13.2.10 (11) Comments and PI Initials	~~13-313-4~~
13.3 MedWatch Form.....	~~13-313-4~~
CHAPTER 14.protocol violations and minor Deviation Form (TOP10)	14-1
14.1 Protocol Violations and Minor Deviations	14-1
14.2 Protocol Violation and Minor Deviation Form – TOP10.....	14-1
14.2.1 Section A. Occurrence of Protocol Violation/Deviation Events During Study Intervention (record Section B once per infant case)	14-1
14.2.2 Section B. Event.....	~~14-114-2~~
14.2.3 Section C. Protocol Violation/Deviation Details.....	~~14-114-2~~
14.2.4 Section D. Event Circumstances	~~14-214-3~~
CHAPTER 15.study Withdrawal form (TOP11)	15-1
15.1 Study Withdrawal Form (TOP11).....	15-1
15.1.1 Section A. Withdrawal	15-1
15.2.2 Section B. Additional Comments	15-1
Appendix A: Sample Consent	A-1
Appendix B: Randomization Script	B-1
Appendix C: Randomization Tracking	C-1
Appendix D: SNAP Score Article	D-1
Appendix E: Toxicity Table	E-1

CHAPTER 1. STUDY OVERVIEW

1.1 Introduction

This manual provides detailed instructions for study procedures related to **Transfusion of Prematures (TOP) Trial**: Does a Liberal Red Blood Cell Transfusion Strategy Improve Neurologically-Intact Survival of Extremely-Low-Birth-Weight Infants as Compared to a Restrictive Strategy? This manual is designed to serve as a reference guide for study staff including investigators, coordinators, technicians and data managers. The trial objectives and design are summarized below.

1.2 Synopsis

The study question is: “In infants who are born at gestational ages of 22 0/7 to 28 6/7 weeks, will the implementation of a higher hemoglobin threshold for transfusing extremely low birth weight (ELBW) infants resulting in higher hemoglobin levels, lead to an improvement in the primary outcome of survival and rates of neurodevelopmental impairment (NDI) at 22-26 months?”

Long-term outcomes of ELBW infants, weighing less than 1000 g at birth, are poor and pose a major health care burden. Virtually all of these infants are transfused, but at inconsistent hemoglobin (Hgb) thresholds. This results from conflicting data regarding when these infants should be transfused, preventing an evidence-based recommendation. However, the Prematures In Need of Transfusion (PINT) study (Kirpalani H 2006) suggests that higher Hgb thresholds for transfusion may be beneficial to long-term neurocognitive outcomes at 18-22 months (Whyte R 2009). If a definitive adequately powered trial verifies this, the potential impact is high. An economic analysis of the PINT study outcomes showed that the increased costs of transfusion in the liberally transfused group would be more than offset by benefits of reduction in poor outcomes at 24 months (Kamholz K [2012](#)). On the other hand, the Iowa RCT showed that any short-term potential neurological benefits of more liberal blood transfusion (Bell EF 2005) were offset by poorer outcomes in brain structure and function at 7-10 year follow-up (Nopoulos P 2011, McCoy TE 2011). This follow up study, however, had a significant attrition making it difficult to understand its’ implications.

We propose in TOP to randomize infants ≤ 1000 g BW and < 29 weeks GA to receive red blood cell (RBC) transfusions according to one of two strategies of Hgb thresholds, either a high Hgb (liberal transfusion) or a low Hgb (restrictive transfusion) algorithm. It is currently unknown which transfusion strategy is superior. TOP is powered to demonstrate which strategy reduces the primary outcome of death or neurodisability in survivors at 22-26 months.

We therefore propose an open, parallel-group multicenter randomized controlled trial (RCT) analyzed by intention to treat. TOP randomizes extremely-low-birth-weight infants (birth weight less than or equal to 1000 g and gestational age between 22 0/7 to 28 6/7 weeks) to either a liberal or a restricted red cell transfusion regimen according to hemoglobin/hematocrit thresholds. Following consent of eligible infants, central randomization will be performed within strata of birth weight (<750 g versus 750-1000 g) and study center, with variable block sizes. Compared to larger preterm infants, ELBW infants are at greater risk of death and neurodevelopmental sequelae. Two previous trials - the PINT trial (Kirpalani H 2006) and its follow-up PINT-Outcome Study (PINT-OS, Whyte R 2009), and the Iowa (Bell EF 2005) trial and its follow up study (Nopoulos P 2011) - raise important but contradictory implications for CNS injury and development. These can only be resolved in a new large trial.

The objective of the TOP trial is to determine whether higher hemoglobin thresholds for transfusing ELBW infants resulting in higher hemoglobin levels lead to improvement in the primary outcome of survival and rates of neurodevelopmental impairment (NDI) at 22-26 months.

1.3 Study Duration

The study intervention will be applied to the enrolled infant up to the postmenstrual age of 36 weeks or until the time of discharge from the NICU or death, whichever comes first. The enrolled infant will remain in the study until the 22-26 month follow-up assessment has been completed.

1.4 Primary Outcome

The primary objective of the TOP trial is to assess the difference in the primary outcome of survival without death or NDI at 22-26 months adjusted age in the two treatment arms.

1.5 Secondary Outcomes

Secondary outcomes include:

- During initial hospitalization:
 - Ultrasound grade 3 or 4 IVH, cystic PVL, or ventriculomegaly;
 - Bell stage 2 or 3 NEC;
 - Apnea mandating either caffeine or respiratory support;
 - Age at final tracheal extubation;
 - Number of donor exposures by RBC donors or other blood product;
 - Number of transfusions;
 - ROP stage 3 or greater or requiring treatment;
 - Time to regain birth weight;
 - Time to full feedings;
 - Death before discharge;
 - BPD at 36 weeks postmenstrual age based on need for oxygen supplementation following an oxygen reduction test;
 - Decreased height, weight, or head circumference at 36 weeks postmenstrual age;
 - Length of hospital stay at Level 3 care; and
 - Costs of hospitalization.
- At 22-26 months corrected age, each of the composite outcomes individually:
 - Moderate or severe cerebral palsy;
 - Severe vision impairment;
 - Severe hearing impairment;
 - BSID-III Cognitive score < 85;
 - BSID-III cognitive, language, or motor score <70;
 - Gross Motor Function level $\geq$ II;
 - CBCL Internalizing, Externalizing, and Total Problems aggregate T scores of $\geq$ 64 (clinical range) and 60-63 (borderline range) will be evaluated
 - Death before 22-26 month follow-up;
 - Decreased height, weight, or head circumference at 22-26 month assessment; and
 - Cost-benefit analysis of primary outcome at 22-26 months

1.6 Study Design

The TOP trial is an open, parallel-group multicenter randomized controlled trial (RCT) analyzed by intention to treat. TOP randomizes extremely-low-birth-weight infants (birth weight ≤ 1000 g and gestational between 22 0/7 to 28 6/7 weeks) to either a liberal or a restricted red cell transfusion regimen according to hemoglobin or hematocrit thresholds. Following consent of eligible infants, central randomization will be performed within strata of birth weight (<750 g versus 750-1000 g) and study center, with variable block sizes.

1.7 Inclusion Criteria

- Birth weight less than or equal to 1000 grams.
- Gestational age between 22 0/7 to 28 6/7 weeks
- Admitted to the center NICU within 48 hours of life
- Ability to randomize within 48 hours

1.8 Exclusion Criteria

- Considered non-viable by the attending neonatologist
- Cyanotic or severe congenital heart disease
- Parents opposed to the transfusion of blood
- Parents with hemoglobinopathy or congenital anemia
- *In-utero* fetal transfusion
- Twin-to-twin transfusion syndrome
- Isoimmune hemolytic disease
- Lack of parental consent
- Prior blood transfusion on clinical grounds beyond the first 6 hours of life
- High probability that the family is unavailable to attend follow-up at 22-26 months.
- Is intended to receive erythropoietin through the neonatal course
- Congenital condition that adversely affects life expectancy or neurodevelopment

1.9 Center Baseline Information

Selected infant identifying information will be entered into the NICHD Neonatal Network's data management system (DMS). A Study Number will be assigned by the study coordinator to each infant screened. The following information is used to identify each infant and is placed as the heading of each study form:

- **Center Number** - The assigned Network center number
- **Site** - Centers with more than one participating hospital also have a site code
- **Study Number** Unique infant identifier assigned by the study coordinator and utilizing the following format; T # # # # . (example T0001 – T9999).
- **Network Number** Record the network number assigned by the GDB. The network number will be available for inborn infants. Infants that are outborn who are randomized and enrolled into the study will also be enrolled in the GDB at the same time. They will be assigned a network number which should be entered on the log when it is available.
- **Mother's Initials** This is used at the convenience of the coordinators and will **not** be transmitted to RTI. Mothers should carry the same initials throughout the study even if her name changes.

1.10 Summary of Data Collection Forms

All infants enrolled into this study will be in GDB. The following information is a summary of each data form. Further details are provided in subsequent chapters as study implementation is discussed in conjunction with guidelines for completion of the data collection forms.

Screening Log - (TOP01)

The purpose of the Screening Log is to facilitate the screening of inborn and outborn infants admitted to the NICU within 48 hours of age, with birth weight ≤ 1000 grams and gestational age between 22 0/7 to 28 6/7 weeks). Selected information on this form will not be entered into the DMS

Eligibility and Randomization Form - (TOP02)

The Eligibility Form collects information on inclusion/exclusion criteria, consent status and randomization. Data on this form will be collected on infants who are entered on the Screening Log (TOP01).

SNAP Score Form - (TOP03)

This form collects clinical variables within the first 12 hours of life to determine the severity of illness – to assign a SNAP score.

Hemoglobin / Hematocrit Log – (TOP04)

This log will record all ordered Hgb or Hct tests. If a particular Hgb or Hct value triggers a transfusion, then please complete both the log and the transfusion form (TOP05).

Transfusion Form – (TOP05)

The transfusion form should be completed for every transfusion that the infant receives until 36 weeks PMA, discharge/death, whichever occurs first.

Growth and Therapy Form – (TOP06)

This log will be completed weekly for all randomized infants.

Head Ultrasound – (TOP07)

This form will collect information on a head ultrasound that is performed prior to randomization, if available.

Economic In-Hospital Questionnaire – (TOP08)

All parents will be asked to complete a questionnaire during the stay in the NICU, ideally between days 14-21.

Adverse Event Form - (TOP09)

This form will be completed for each reportable adverse event that randomized infants experience from the time of each transfusion up to 96 hours after each transfusion.

Protocol Violation and Minor Deviation Form - (TOP10)

This form will be completed for all randomized patients whenever a protocol deviation/violation is encountered.

Study Withdrawal Form – (TOP11)

This form will be completed for all randomized patients who withdraw from the study.

CHAPTER 2. ADMINISTRATION

2.1 Study Organization

The NICHD Neonatal Research Network is conducting this study. The Network is funded by the NICHD under cooperative agreements with nineteen institutions, comprising 18 Clinical Centers and a Data Coordinating Center (DCC). The Steering Committee for the Network consists of the Principal Investigator from each Clinical Center, the DCC, and the NICHD Project Officer. The Steering Committee Chairman, who is not participating as a principal investigator from any of the clinical sites, is appointed by the NICHD.

2.2 The TOP Trial Subcommittee

The TOP Trial subcommittee is responsible for the preparation and maintenance of the Protocol, Manual of Operations and data forms. Members of this subcommittee are:

Haresh Kirpalani, BM, MSc (Chair)	Ed Bell, MD (V. Chair)
Carl D'Angio, MD	Kathleen Kennedy, MD, MPH
Susan Hintz, MD	Robin Ohls, MD
Brenda Poindexter MD, MS	Kurt Schibler, MD
Barbara Schmidt, MD	Betty Vohr, MD
Jack Widness, MD	John Zupancic, MD, PhD
Rose Higgins, MD	Abhik Das, PhD
Robin Roberts, MSc	Robin Whyte MD,
Karen Johnson, BSN	Aasma Chaudhary, BS, RRT

2.3 Participating NICHD Neonatal Research Network Centers

18 centers from the NICHD Neonatal Research Network participating in the trial are listed below. The NICHD center number is indicated in parentheses next to the name of each center, the principal investigator is located in the second column and the study coordinators is located in the third column.

Case Western Reserve Univ. (3)	Michele Walsh, MD	Nancy Newman, RN
University of Texas- Dallas (4)	Myra Wyckoff, MD	Diane Vasil, RN
Wayne State University (5)	Seetha Shankaran, MD	Becky Bara, BSN
Emory University (9)	Barbara J. Stoll, MD	Ellen Hale, BS, RN, CCRC
University of Cincinnati (11)	Kurt Schibler, MD	Cathy Grisby, BSN, CCRC
Indiana University (12)	Greg Sokok, MD	Diane Herron, BSN, CCRC
Brown University (14)	Abbot Laptok, MD	Angelita Hensman, BSN, RNC
Stanford University (15)	Krisa Van Meurs, MD	M. Bethany Ball, BS, CCRC
University of Alabama (16)	Waldemar A. Carlo, MD	Monica Collins, RN, MaEd.
University of Texas- Houston (18)	Kathleen Kennedy, MD	Georgia McDavid, RN
Duke University (19)	Ronald Goldberg, MD	Joanne Finkle, BSN
University of Iowa (24)	Edward Bell, MD	Karen Johnson, BSN
University of New Mexico (26)	Kristi Watterberg, MD	Conra Lacy, RN
University of Pennsylvania (27)	Barbara Schmidt, MD	Aasma Chaudhary, BS RRT
University of Rochester (28)	Carl D'Angio, MD	Holly Wadkins, MA
University of California – LA (29)	Uday Devaskar, MD	Rachel Geller, BSN
Nationwide Children's Hospital (30)	Pablo Sanchez, MD	Patty Luzader, RN
Children's Mercy Hospital (31)	William Truog, MD	Cheri Gauldin, BSN

2.4 Responsibilities of the Clinical Centers, the DCC and the NICHD

The roles and responsibilities of the NRN Clinical Centers, the Data Coordinating Center and NICHD program staff are outlined in the NRN Policy and Procedures Manual. This document is located on the private gateway of the NRN website.

CHAPTER 3. SCREENING LOG (TOP01)

3.1 Screening Log – Form TOP01

The purpose of the Screening Log is to record all inborn infants and outborn infants admitted to the center NICU in the first 48 hours of life, with a birth weight ≤ 1000 grams and gestational age between 22 0/7 to 28 6/7 weeks. The Network Coordinator, or her/his designee, enters daily onto the log the infant's screening information:

Infant's Name (Last, First)

Record the infant's name using the format of last name first followed by the infant's first name. *This will not be entered into the DMS.*

Hospital Number

Record the infant's medical record number or other identifying hospital number. *This will not be entered into the DMS.*

Date of Birth

Record the infant's date of birth. This information is entered into the DMS on the base record and transmitted to RTI.

Birth weight

Record the infant's birth weight in grams, this must be ≤ 1000 grams.

Gestational Age

Record the network definition of the infant's gestational age in weeks and days. Weeks may be from 22 through 28, days may be from 0 to 6.

Study Number

Record the unique infant identifier assigned by the study coordinator and utilizing the following format; T # # # #. (example T0001– T9999).

Network ID

Record the Network ID assigned by the GDB. The network number will be available for all inborn infants. For all outborn infants who are randomized and enrolled into the study will also be enrolled in the GDB at the same time. They will be assigned a network number which should be entered on the log when it is available. A complete set of GDB baseline and outcome data will be collected on all randomized infants. The Network number is made up of up to a five digit Family (Pregnancy) Number plus the Birth Order Number. Therefore the Network Number can be up to 6 digits.

Comments

This section may be used for any comments related to the infant. This section will not be keyed.

A **TOP02 Eligibility Form** must be completed for all infants listed on the screening log.

CHAPTER 4. ELIGIBILITY FORM (TOP02)

4.1 Eligibility Form TOP02

This form should be completed for all infants entered on the Screening Log (TOP01). The form is designed to be completed from the top down.

4.1.1 Section A. Inclusion Criteria

In order for an infant to be eligible for this study, all of the inclusion criteria listed below must be answered yes. Provide yes or no responses for the following inclusion criteria:

1. Birth weight ≤ 1000 grams?
2. Gestational age between 22 0/7 - 28 6/7 weeks?
3. Admitted to the center NICU ≤ 48 hours of age?
4. Ability to randomize by 48 hours of life?

If the infant does not meet all Inclusion Criteria, he/she is **not eligible** for randomization.

4.1.2 Section B. Exclusion Criteria

In order for an infant to be eligible for the study, all of the exclusion criteria listed below must be answered no. Provide yes or no responses to the following exclusion criteria:

1. Considered non-viable by the attending neonatologist?
2. Cyanotic or severe Congenital Heart Disease?
Examples include but are not limited to: hypoplastic left heart syndrome, Tetralogy of Fallot, VSD, interrupted aortic arch, coarctation of the aorta, Ebstein's anomaly, truncus arteriosus, transposition of the great arteries, anomalous pulmonary venous return
3. Parents opposed to the transfusion of blood?
4. Parents with hemoglobinopathy or congenital anemia?
It is not possible to have a completely accurate diagnosis of a hemolytic tendency at the time of enrolment. However to minimize the risk of enrolling a baby at high risk of a hemolytic disorder, assessing whether one or two parents have a pre-disposing condition is useful, and the following situations should be considered as exclusions:
 - i) If both parents each have known clinical Sickle Cell (SC) double recessive allele (ie full blown disease); in this case, the baby gets 1 allele (trait) from each and therefore is at high risk of having SC disease.
 - ii) If both parents have any other known hemoglobinopathy of recessive inheritance (including Hemoglobin E or beta-thalassemia).
 - iii) In situations where either the mother or father has a known autosomal dominant disorder (eg Hereditary spherocytosis) the inheritance leads to a 50% chance of the child having the same disorder.
5. In-utero fetal transfusion?
6. Twin-to-twin transfusion syndrome?

This can be documented either in the neonatologists' admitting notes or in the obstetricians notes.

7. Isoimmune hemolytic disease?

Relevant examples include Rh erythroblastosis and ABO isoimmunization with positive direct antiglobulin (Coombs) test or evidence of abnormal hemolysis on blood smear.

8. Any blood transfusion ordered between 6 hours of life and time of randomization?

Record 'Y' if infant had any red blood cell transfusion ordered between 6 hours of life and randomization.

If the infant received a transfusion of platelets, please record 'N'. Infants receiving a platelet transfusion between 6-48 hours are not excluded.

Timing of the blood

The 6 hour window enabling blood to be given for emergent perinatal loss of blood includes written orders that are within the 6 hours. Hence if for whatever reason the blood bank delivery of blood is delayed until after that 6 hours, or if the blood has been started within the 6 hours but is not completed – that baby is still eligible.

9. Unlikely that family will be available for follow-up at 22-26 months?**10. Did patient receive erythropoietin or is going to receive erythropoietin?****11. Congenital condition, other than prematurity, that adversely affects life expectancy or neurodevelopment**

Record 'Y' if the infant is diagnosed with any congenital condition, including chromosomal and non-chromosomal abnormality; congenital infection; neurologic or other disease known at the time to adversely affect life expectancy or neurodevelopment. This may or may not be also considered an issue of viability.

4.1.3 Section C. Consent

Parental consent must be obtained before the infant can be enrolled and randomized. A signed consent form must be on file for each infant prior to requesting randomization into this study. A sample consent form can be found in **Appendix A**.

1. Consent Status:

Select the appropriate consent status

Not eligible (if one or more of the inclusion criteria questions are answered "No" the infant is ineligible. If one or more of the exclusion criteria are questions are answered "Yes" the infant is ineligible.)

Consent granted (if parental/guardian consent is obtained for study enrollment).

Parent refused consent (if a parent or legal guardian refuses consent for study enrollment).

Parent refused consent, not willing to randomize multiples separately (if the parent is concerned about randomizing the multiples to possible different treatments).

Parent unavailable (if the parent or legal guardian is unavailable throughout the eligibility period). Please indicate reason.

Parent not approached (language or social problems as well as deaths before parents are approached). Please indicate reason.

Physician refused consent (if the infant was eligible for the study, but the physician refused to consider the baby for randomization). Please indicate reason.

Infant died prior to consent

Other. Please indicate reason.

- a. **If parent unavailable, parent not approached, physician refused consent, or other indicate reason:**

Specify the reason consent was not requested.

4.1.4 Section D. Randomization

Complete this section for all eligible infants whose consent was granted.

1. **Was the infant randomized into the study?**

Code 'Y' if the infant was given a randomization number and treatment assignment via the telephone randomization system.

- a. If No, select the reason why the infant was eligible but not randomized. The form is complete

Parent withdrawal of consent

Physician refusal to randomize

Infant died prior to randomization

Research staff unavailable

Other (Specify) _____

If the infant was randomized, answer the following:

- b. **Date of randomization:**

Enter the date the actual call to randomize an infant was made and the randomization assignment was obtained.

- c. **Time of randomization:**

Enter the time the actual call to randomize an infant was made and the randomization assignment was obtained. Use 24 hour format in hours and minutes. If you forget to record the time of randomization, please contact NRN Protocol Support at NRNProtocolSupport@rti.org.

- d. **Birth weight strata:**

Select the birth weight strata used to randomize the infant

< 750 grams

OR

750-1000 grams

- e. **Randomization Number:**

Enter the randomization number that was assigned from the telephone randomization system.

f. **Randomization Assignment:**

Select the randomization assignment that was assigned from the telephone randomization system:

High Transfusion Threshold

OR

Low Transfusion Threshold

4.1.5 Section E. Data between birth and randomization

Complete this section for all randomized infants.

1. Did the baby have a documented delayed cord clamping?

2. Did the baby have documented cord milking?

3. Was surfactant given between birth and randomization?

4. Any supplemental oxygen (> 21%) at time of randomization?

5. Any positive airway pressure (including CPAP, NIMV, NIPPV, SiPAP, MV and any NC flow > 0.5 lpm) at time of randomization?

Nasal cannula with a flow rate that is > 0.5 lpm is considered “positive airway pressure”.

MV – mechanical ventilation. This includes invasive as well as non-invasive ventilation.

a. If yes, was an endotracheal tube in place?

Please specify if infant is intubated (yes or no).

CHAPTER 5. RANDOMIZATION PROCESS

5.1 Randomization

Randomization will occur only for eligible infants from whom parental consent has been obtained. *Multiples will be randomized separately.*

5.2 Telephone Randomization System:

The Neonatal Research Network Telephone Randomization System will be accessed by the Study Coordinator or their designee. This system is set up to run every day, 24 hours a day, for the duration of the study. The automated telephone system asks for a 4-digit password to keep unauthorized persons from accessing the randomization assignments.

Before calling the randomization system, the person calling should make sure that they have all of the following information available:

- 4- digit center password
- Consent status
- Birth weight (must be ≤ 1000 grams)
- 4-digit Study Number (from the TOP01)

5.2.1 Calling the Randomization System

When an infant is deemed eligible and the assigned person is ready to randomize the infant, he or she should call the RTI telephone randomization system at 1-800-262-2673. If a busy signal is heard, the system is currently being accessed by another center. Randomization calls last 1-2 minutes.

If for any reason the randomization system is unavailable call the 24/7 emergency randomization phone number 1-866-253-1624 and a programmer at RTI will be able to assist you with the randomization.

5.2.2 The Randomization Process

Once the system answers, the caller will be asked a series of questions. The caller is instructed to use the system at each step of the way. The script is shown in **Appendix B**. The caller should wait for the question to be stated completely before keying in the answer or “typing ahead”. This reduces the likelihood of keying errors. The system will wait 5 seconds after the end of each question for the answer. If no answer is received within 5 seconds, a warning is issued and the question is asked again. **The baby is randomized when the caller receives the randomization number and the randomization assignment.**

Note: The caller must be aware of when it is safe to hang up. Except in the case of a keying error when the caller intends to cancel the randomization process, he or she should not hang up before receiving the final “Thank you and Good-bye” from the system. If the caller does hang up early, he or she should wait about 20 seconds before calling again to give the system a chance to reset. Calling back too soon will result in a busy signal.

At this point, the randomization number and assignment should be recorded on the TOP02 form by the study coordinator.

5.3 Randomization Tracking Tool

A randomization tracking tool is located in **Appendix C**. This tool is provided to track randomization (if desired), similar to a randomization log. This tool will not be keyed.

CHAPTER 6. SNAP SCORE FORM (TOP03)

6.1 SNAP Score Form (TOP03)

This form should be completed for all randomized infants. In order to correct for potential confounders for the primary outcomes, clinical measures will be collected to calculate the SNAP Score. This is a validated index of severity of illness. All the components of the necessary data are standard routine clinical measurements or observations. None of these are specific to this study protocol. For each physiologic measure, record the lowest value obtained in the first 12 hours of life. The SNAP score will be computed by RTI. In the Appendix is a recent re-validation paper for the score, which also shows that further details as required by the SNAP do not add further meaningful discrimination. For more details about the SNAP Score, see **Appendix D**.

6.1.1 SNAP Measurements

For each of the following physiologic measurements, record the lowest value for each physiological measurement obtained in the first 12 hours of life.

1. Lowest mean blood pressure (mm Hg).

The exact method of obtaining this value is not relevant for SNAP. Please record the lowest mean blood pressure available.

2. Lowest temperature (°C) or (°F)

Record lowest temperature using whatever clinical method is currently used in your nursery.

3. Lowest PaO₂ (mmHg)

Arterial measurement preferred, if not available record capillary or venous.

4. Corresponding FiO₂ (%) for the lowest PaO₂ as recorded in question 3 above..

5. Lowest Serum pH (includes cord gas)

6. Multiple Seizures

If the infant had multiple (more than 1) suspected or documented seizure, please select the “multiple seizures” option. If there were no seizures or only 1 (suspected or documented), then select “none/single”.

Seizure activity does not need to be proven by EEG recording to be considered a documented seizure. Any seizure that is documented by a nurse or clinician is considered a “seizure” in terms of the SNAP score.

7. Urine Output (ml)

Record the total milliliters of urine in the first 12 hours. If there is no urine in the first 12 hours, record zero. RTI will compute this as ml/kg/hr

CHAPTER 7. TRANSFUSION TRIGGERS ALGORITHMS

7.1 Overview

Infants will be randomized to either a liberal or a restricted red cell transfusion regimen according to hemoglobin/hematocrit thresholds. The decision to transfuse will be based on postnatal age and respiratory status.

The use of postnatal age to define transfusion thresholds in clinical practice has been historically based on the physiologic fall in hemoglobin seen in infancy. Respiratory support is defined as one of the following: mechanical ventilation, continuous positive airway pressure, F_iO_2 in excess of 0.35, or by nasal cannula ≥ 1 liter per min. For further clarity, please follow the series of steps as outlined below. The final intervention algorithm reflects substantial dialogue with all NRN site members. It will be applied to the enrolled population up to the postmenstrual age of 36 weeks or until the infant is discharged from the NICU, or death (whichever occurs first).

In the remaining sections of this chapter we present both algorithms for high and low thresholds. Since some NICUs prefer to use hematocrit, we provide the table by HCT also, using the conversion formula: Hematocrit (%) = $2.941 \times \text{Hgb (g/dl)}$. Every NICU varies according to whether to use hemoglobin or hematocrit. Please only use one trigger (hemoglobin or hematocrit) for all data entry on the Hemoglobin Log (TOP04).

The decision to transfuse is determined in a series of steps:

(1) Respiratory Status

The following are defined as respiratory support:

ETT Invasive ventilation

Non-invasive ventilation (NCPAP, NIMV, NIPPV or SiPAP, etc.)

Nasal Cannula ≥ 1 lpm regardless of FiO_2

Nasal Cannula < 1 lpm IF $FiO_2 > 35\%$

Oxygen hood with $FiO_2 > 35\%$

The following are defined as non-respiratory support:

Nasal Cannula < 1 lpm and $FiO_2 \leq 35\%$

(2) Determine the postnatal age of the infant (DOB = day of life 1):

Day of life 1-7 is considered week 1

Day of life 8-14 is considered week 2

Day of life 15 to discharge / death is considered weeks ≥ 3

(3) Transfuse once the hemoglobin or hematocrit falls to or below the respective trigger.

In addition please note :

The decision regarding transfusion is based on respiratory support at the time the Hgb/Hct is drawn. If, at that time, there is an active order in place for some kind of scheduled intermittent/cycled support using something that qualifies as respiratory support, the baby should be considered to be on

respiratory support for the purpose of the transfusion decision. (It doesn't matter whether they happened to be cycled on or cycled off at the time the Hgb/Hct was drawn).

7.2 High Threshold Algorithm

If the infant is randomized to the high threshold algorithm, adhere to the following algorithms.

High threshold algorithm (hemoglobin)		
	Respiratory Support	No Support
Period:		
Week 1	13.0	12.0
Week 2	12.5	11.0
Weeks ≥ 3	11.0	10.0

High threshold algorithm (hematocrit)		
	Respiratory Support	No Support
Period:		
Week 1	38.0	35.0
Week 2	37.0	32.0
Weeks ≥ 3	32.0	29.0

7.3 Low Threshold Algorithm

If the infant is randomized to the low threshold algorithm, adhere to the following algorithms.

Low threshold algorithm (hemoglobin)		
	Respiratory Support	No Support
Period:		
Week 1	11.0	10.0
Week 2	10.0	8.5
Weeks ≥ 3	8.5	7.0

Low threshold algorithm (hematocrit)		
	Respiratory Support	No Support
Period:		
Week 1	32.0	29.0
Week 2	29.0	25.0
Weeks ≥ 3	25.0	21.0

7.4 Ordering and Giving the Blood Transfusion

We do not require that there be mandatory blood test checks for hemoglobin. However, we do ask for speedy adherence to algorithm, such that once a transfusion trigger has been reached, blood must be ordered for transfusion. The procedure for blood transfusion and the preparation of the blood used will be the same as

that regularly used by your site. In all clinical sites special care must be taken to ensure that the decision to transfuse is compliant.

7.5 Time Interval Between Reaching the Trigger Threshold and Receipt of Blood

There are two situations: (i) At randomization: Once a baby is randomized, check to see if the baby meets the trigger for a transfusion based on previous hemoglobin or hematocrit values obtained since the time of birth. If the baby does meet the criteria, then a blood transfusion should be ordered based on the most recent previous CBC results. This is consistent with our intent not to perform additional testing over and above clinical testing. (ii) For all CBC results after randomization, this transfusion should be as early as possible – but at least within 12 hours of reaching a hemoglobin threshold. This applies even if the parents have opted for direct donation and this is not yet available from the blood bank. Delays in this availability usually extend from 24-48 hours. All transfusions will be given as per standard unit policy, which usually means over 2-4 hours.

If for whatever reason there is a delay beyond 12 hours and it is recognized later, the transfusion should still be given. The time is recorded as usual. If there has been an interval lab check of hemoglobins and the threshold has in fact not been reached, the transfusion can be withheld.

7.6 Volume of Transfusions and Hemoglobin Measures

We will use a standard transfusion volume of 15 ml/kg. A fixed transfusion volume will yield higher compliance and a consistent difference in Hgb levels between the two arms. Centers are free to obtain blood samples for Hgb determination from venous, arterial, or prewarmed heel capillary blood according to vascular access and their usual practice. We recognize that values from large veins and arteries are systematically lower than capillary samples by about 8.5% (Blanchette VS 1984). However for a pragmatic trial, these small differences are not problematic and do not require adjustment. We will not mandate Hgb checks, but by polling we have ensured that most units obtain these at least weekly in the first month. We will record all Hgb values obtained on the Hemoglobin / Hematocrit Log (TOP04).

7.7 Clinically Driven Transfusions or Algorithm Deviations

The algorithm will determine transfusion for routine or “top-up” transfusions, but additional transfusions may be given for infants with urgent need for transfusion. These are **largely** because of bleeding or anticipated bleeding (e.g. during and after surgery), shock, coagulopathy, severe sepsis possibly with hemolysis etc. **All blood transfusions will be recorded and categorized as:** (1) **per randomization scheme, Hgb/Hct trigger;** (2) **bleeding;** (3) **perioperative or pre-op (often driven by anesthetic wishes);** (4) **exchange transfusion, indicate reason;** (5) **clinician preference due to patient severity of illness , specify (e.g., shock, severe sepsis with coagulopathy, severe hypoxemia with massive ventilation requirements, severe hypotension;** (6) **other indication: specify.** All subsequent events will be analyzed by intention-to-treat principles, irrespective of additional transfusions, trial dropouts, or protocol violations. Rates of non-algorithm transfusions will be monitored.

Please refer to Chapter 14 for protocol deviations (including triggers that were met, but no transfusion was administered).

7.8 Maintaining Adherence to Algorithm and Minimizing Deviation from Protocol

As noted above, the algorithm will drive the majority of the transfusions. In exceptional circumstances, as defined in 7.7, the algorithm may be set aside until the infant is deemed stable to allow resumption of transfusion by study algorithm. For instance, after an operation, and when the clinician judges the infant has stabilized. **Examples** of such temporary situations are infants with shock, severe sepsis with coagulopathy; or need for perioperative transfusion, where the clinical indication for transfusion will override the algorithm-set threshold. Another possible scenario is very serious hypoxemia with massive ventilation requirements. However we caution that the role of blood transfusion in this latter possible example, is conjectural. It should prompt a local re-discussion about the threshold values. In the PINT multicenter trial, the rate of deviation from protocol was acceptably low (15.9% in the low threshold arm and 6.7% in the high threshold arm). We assess adherence and separation of arms by recording mean Hgb at transfusion and at discharge. No Hgb determinations are mandated by study, but only as clinically ordered.

7.9 Checking and Maintaining Compliance at the Bedside

The research staff will place notification on the infant's bed, or in a prominent position (e.g. perhaps on the incubator), that contains the designated threshold trigger and transfusion algorithm (i.e. clearly stating this infant has been randomized to the TOP trial and is in the "LOW" threshold; or the HIGH threshold"). It is often helpful to print and laminate the cards for the two thresholds, and give the relevant one to the nurse looking after the infant; and distribute these to the clinical teams. Inform parents to which their arm the baby has been randomized, often they will also serve to be guardians of the algorithms.

7.10 Direct Donors

Established practices of the Neonatal unit with regard to direct donor status are not affected by this trial and should continue. Currently in some units that do practice a policy of direct donation, there is a delay that occurs during which time the parents have to be tested and it is ensured that the parents are 'eligible' for donation. This, of necessity, may take 24-48 hours. (See point 7.5)

7.11 Transfusions and Blood Banking

All RBCs transfused will be tested and screened according to the policies of the blood banks serving each hospital participating in the trial. These practices will be recorded throughout the trial, with notification to the DCC of any policy changes. The blood transfused will be ABO and Rh compatible with the infants' type. Individual unit practices related to blood transfusion vary among the participating sites. Because randomization will be stratified by site, variation in local blood banking practices will not result in imbalances between treatment groups and will allow greater generalizability of the study results. The details of blood bank practice to be recorded for each site will include screening for CMV, storage buffer, maximum storage age, policies for RBC washing and leukoreduction, and methods of

storing and concentrating RBCs. The age of donor blood will be recorded for each transfusion, but there is no restriction on age beyond individual site practice.

CHAPTER 8. HEMOGLOBIN/HEMATOCRIT LOG (TOP04)

8.1 Hemoglobin and Hematocrit Log Overview (TOP04)

A log of all ordered hemoglobin/hematocrit tests will be maintained from the time of birth until 36 weeks PMA, death or discharge, whichever occurs first. Once the infant reaches 36 0/7 weeks, hemoglobin/hematocrits do not need to be documented. Once a baby is randomized, please check to see if previous hemoglobin/hematocrit values met the criteria for a blood transfusion. If a trigger was met, then a blood transfusion should be administered.

By ordered hemoglobin, is meant hemoglobins that are specifically drawn from the infant to be sent to the hematology lab. If a blood transfusion is ordered based on a blood gas hemoglobin or hematocrit, please enter this particular blood gas on the log. All other blood gases - that do not trigger a blood transfusion - do not need to be recorded on the log.

The study does not mandate when hemoglobin/hematocrit values should be measured, each center should follow their standard of care. But a minimum of one weekly measure is expected.

8.1.1 *Completing the Log*

For each hemoglobin/hematocrit value ordered, record the following:

1. Test Number

Record the test number. This test # will link transfusions on the TOP05.

2. Date

Record the date of the test.

3. Time

Record the time of the test.

4. Hemoglobin or Hematocrit

Record the hemoglobin value in g/dL and/or record the hematocrit value in %. For hemoglobins we believe all labs report to the first decimal place, and this should be recorded as such. For hematocrits, practice appears to vary by site – such that some sites will record only a full integer, whereas others will report to the first decimal place. If your site reports by decimal place please report in that way; for example, 34.5 % will be entered as 34.5. You need enter only one value (either as hemoglobin or hematocrit), but you can enter both if ordered in the same test.

Finally, and most importantly, if the hemoglobin/hematocrit result led to a decision to transfuse, this should be recorded on the TOP05, detailed in the chapter below. This is the most important measure of compliance.

If a value indicated a transfusion based on the algorithms detailed in Chapter 7, but the infant was NOT transfused, please complete a Protocol Violation/Minor Deviation Form (see chapter 14).

In these instances please follow up with the clinical teams to remind them of the study and the algorithms.

5. Source

Please indicate if the hemoglobin/hematocrit entered on the log was from a CBC, as part of a blood gas or other. If a blood transfusion is ordered based on a blood gas hemoglobin or hematocrit, then enter this particular blood gas on the log. All other blood gases that do not trigger a blood transfusion do not need to be recorded on the log

CHAPTER 9. TRANSFUSIONS AND TRANSFUSION LOG (TOP05)

9.1 Transfusion Overview

Once a transfusion trigger has been reached (see Chapter 7), blood must be ordered for transfusion. The procedure for blood transfusion and the preparation of the blood used will be the same as that regularly used by each site. All red cells transfused are tested and screened according to the policies of the blood banks at each site. The blood transfused is ABO and Rh compatible with the infants' type. Each site has standardized details of blood transfusion such as the practice of direct donation; leukocyte depletion; age of blood transfused, washing blood etc. The TOP Trial does not change any of those. Each site will continue to screen all blood for HIV and hepatitis.

9.2 Transfusion Log (TOP05)

A record of all transfusions, that includes transfusions initiated per the algorithms and also per clinical care, from the time of birth until 36 weeks PMA, death or discharge, whichever occurs first, should be maintained.

9.2.1 Section A: RBC Transfusion Record

For each transfusion, record the following:

1. Date

Record the date of the transfusion.

2. Donor Unit ID

3. Aliquot Number

4. Weight

Record the infant's last known weight up to the time of the transfusion

5. Blood Source

Select the blood source for the transfusion:

Blood Bank (non-directed)

OR

Directed Donor

6. Volume Given (mL)

Record the transfusion volume in mL.

7. Is infant receiving enteral feeds?

The reason to collect this is that practice variation has been informed by a recent controversy on whether blood transfusions "causes" NEC. Available data is in marked conflict, and the TOP trial may be able to assist clarification.

Record 'Y' if at the time a transfusion is indicated, the infant is receiving enteral feeds.

If yes,

a. If yes, were enteral feeds withheld during this transfusion?

8. Reason for the transfusion

Select all the reason(s) why the transfusion was initiated:

As per randomization scheme, Hgb/hematocrit trigger – if this is selected, also record the test number that triggered this transfusion from column 1 of the TOP04. Please record the first test number that triggered this transfusion. Do not record a hemoglobin/hematocrit that was measured after a trigger was reached.

Allowable per protocol

Bleeding

Pre/intra/post-operative

Exchange transfusion, indicate reason

Severe Sepsis

Severe Hypotension

Severe Hypoxemia with large increase FiO₂/repiratory support

Prior to randomization or post withdrawal

Not allowable per protocol – If a reason below is selected please also complete a TOP10 form.

Clinician preference, indicate detailed reason:

Other, specify

9. Is infant currently receiving caffeine or methylxanthine?

9.2.2 Section B: Clinical Variables Prior, during and after the transfusion

Clinical variables need to be recorded at set time intervals. The list of variables is as follows:

1. Start Time

Record the time the transfusion was initiated.

2. End Time

Record the time the transfusion was complete.

3. Did a new IV have to be established to deliver this blood transfusion?

Record 'Y' if a new IV was established for the purposes of this transfusion

For the variables listed below, please record values at the following time points.

- *Prior to transfusion – at any point 1-6 hours prior to transfusion for the particular clinical parameter*
- *Start of transfusion*
- *6 hours after the end of transfusion – at any point*

4. Lowest mean blood pressure, mmHg

Record the lowest mean blood pressure as a 2 digit number. For example, mean BP of 25 will be entered as 25.

5. Highest heart rate per minute

Please record this as a 3 digit number. For example, HR of 134 will be entered as 134

6. Highest respiratory rate per minute

Please record the highest spontaneous respiratory rate per minute. If infant is invasively or non-invasively ventilated please record the highest respiratory rate per minute (add the spontaneous breaths and ventilator supported breaths together).

Please record this as a 3 digit number. For example, RR of 79, will be entered as 079

If the infants is on HFO or HFJV the “highest spontaneous respiratory rate” may be omitted.

7. Highest supplemental oxygen (includes NC)

If yes, please record the FiO_2 as a 2 digit number. For example, 34 % will be entered as 34

8. Lowest SpO_2

Please record this as a 2 digit number. For example 92 %, will be entered as 92.

9. Highest CPAP cm H_2O

If the infant is receiving non-invasive CPAP, please record the CPAP setting .

If the infant is on RA or nasal cannula (including high flow nasal cannula), then leave the field blank. For the purposes of TOP, the CPAP category has been simplified to just CPAP/PEEP delivery via mask/prongs. If the SiPAP machine is being used to deliver PEEP and oxygen only, this is considered CPAP.

10. Intermittent positive pressure ventilation (IPPV) (if yes, highest MAP)

If no, then please record, N.

If yes, the infant is receiving noninvasive or invasive intermittent positive pressure ventilation, then please record “yes” and the highest mean airway pressure (MAP) setting.

Examples of noninvasive intermittent positive pressure ventilation include NIMV or NIPPV and SiPAP.

SiPAP is the name of the device that can administer two different modes of non-invasive ventilation: (1) CPAP and (2) bi-phasic mode.

If the SiPAP device is being used to deliver CPAP, please enter “yes” for question 9 and record the PEEP level. Hence, the field for question 10 will be “no”.

If the SiPAP device is being used in the bi-phasic mode, there were will be two different levels of PEEP and a rate. For the purposes of this trial, this mode will be categorized as non-invasive IPPV. Please enter “no” for question 9. Please enter “yes” for question 10.

If a rate is being used then this is NOT simple CPAP. For the purpose of the TOP trial, PEEP with a rate should be coded as IPPV.

11. High Frequency Ventilation (HFV) (if yes, highest MAP)

If no, then please record, N.

If yes, the infant is on HFOV or HFJV then please record “yes”. If the infants is on HFOV or HFJV the “highest spontaneous respiratory rate” data field should remain blank. Please record MAP, FiO₂, SpO₂.

12. Inotropic support

Please record Y or N for each time interval requested. An infant who was not on inotropic support prior to the transfusion could possibly require inotropic support during the transfusion. Inotropic support is any drug given for blood pressure.

13. Apnea (requiring more than mild tactile stimulation).

Regular bedside observation and recording of apnea is often subjective, and as this trial is unblinded, it is subject to bias and over- or under-estimation of apneic events. The TOP Trial does not dictate how centers should record apnea or its prevention and treatment. We simply ask that apnea requiring more than mild tactile stimulation be recorded as yes/no. For this purpose consider ‘mild’ to be simple rubbing, gentle movement of limbs.

The need for bag-mask ventilation and/or CPAP would be considered “more than tactile stimulation”.

14. Nurse: infant ratio (highest nurse to infant ratio during transfusion)

Record the highest nurse to infant ratio during the transfusion. 1 nurse to 4 infants is higher than 1 nurse to 2 infant

CHAPTER 10. GROWTH AND THERAPY FORM (TOP06)

10.1 Growth and Therapy Form – TOP06

The Growth and Therapy Form must be completed for all infants randomized

10.1.1 Section A: Growth Data

For each week the infant remains in study (date of randomization through 36 weeks, death or discharge whichever occurs first), complete this section.

1. Week of life

This field is pre-populated.

2. Body Weight

Record the infant's body weight in grams for each week of life they remain in the study.

3. Head circumference

Record the infant's head circumference for each week of life they remain in the study. The head circumference should be measured by consistent staff and represents the consistent greatest occipito-frontal circumference that can be obtained with 3 attempts of repositioning the tape measure.

10.1.2 Section B: Therapy Data

Complete this section for all randomized infants.

1. Was the infant ever started on caffeine?

a. If yes, was the infant still on caffeine at status (36 wk PMA, death or discharge)?

i. If no, date of final caffeine dose?

Record the last date the infant received caffeine.

2. Did the infant ever have an endotracheal tube?

a. If yes, was the infant still intubated at status (36 wk PMA, death or discharge)?

i. If no, date of final tracheal extubation

Record the date of final tracheal extubation, the last day that the baby required an endotracheal tube.

CHAPTER 11. HEAD ULTRASOUND FORM (TOP07)

11.1 Head Ultrasound Form– TOP07

This form will be completed for all randomized infants. This form will collect information on a pre-randomization HUS, **only** if this is available per clinical orders. The TOP trial does not mandate a pre-randomization HUS.

11.1.1 Section A. Pre-randomization HUS Results

1. Was a pre-randomization HUS performed?

If no, form is complete.

If yes,

a. Date of the Study

Record the date of the pre-randomization HUS reading.

2. Was the HUS normal?

Record yes or no.

If yes, form is complete. If no, complete 2.a.

2a) if yes, check all that apply:

These can occur on either side or both.

1. Subependymal hemorrhage
2. IVH with or without ventricular dilatation
3. Intraparenchymal echodense lesion
4. cerebellar hemorrhage
5. cystic PVL (periventricular leukomalacia)
6. porencephalic cyst
7. ventriculomegaly
8. other, specify

CHAPTER 12. IN-HOSPITAL COST OF CARE QUESTIONNAIRE (TOP08)

12.1 In-Hospital Cost of Care Questionnaire – TOP08

An important secondary outcome of the TOP trial is an economic cost-benefit analysis to time of discharge and to 22-26 month follow-up. During the infant's initial hospitalization, the parent(s) or legal guardian of the infant will be asked to complete a questionnaire about the costs of caring for their infant.

12.1.1 *Administering the questionnaire*

This questionnaire will be detailed in the consent form signed by the parent(s) or legal guardians(s). Please complete the shaded area at the top of each questionnaire with the Study ID before giving it to the parent or legal guardian for completion. Ideally, the parent will complete the questionnaire while they are at the clinical site (rather than taking it home).

The In-Hospital Economic Evaluation should be completed by a parent or legal guardian once during the NICU stay, ideally between days 14 and 21. The time frame in which to complete the questionnaire is flexible, as long as it is completed prior to discharge.

12.1.1 *Data entry*

After the questionnaire is completed, it will be entered into the DMS. In addition to each response that is listed on the form, you will have the ability to select "This question was skipped by parent/guardian in the data entry system".

CHAPTER 13. ADVERSE EVENT FORM (TOP09)

13.1 Adverse Event Form – TOP09

Complete this form for all randomized infants. This form should be completed devoid of any names and hospital record number, if a randomized infant experiences an adverse event and email a pdf to higginsr@mail.nih.gov and NRNProtocolSupport@rti.org or fax to RTI at 919-485-7762 and Rosemary Higgins, MD at the NICHD 301-496-3790 by end of business next working day. If an event has not been resolved within that time, send the incomplete form with the date and time of onset and as much other information as possible. Amend the incomplete form as soon as the adverse event resolves or at the end of the status, whichever comes first, and send to RTI and the NICHD again.

13.2 Instructions for Completing the Adverse Event Form

Complete the identification codes on the header on each page of the form with the Center number, Site designation, unique Study Number assigned to this subject, Network ID. Use of Mother's Initials is optional.

Are there any adverse events to report for this infant?

If no, this form is now complete.

If yes, proceed to record each adverse event on a separate form. This lead-in question must only be answered on the first form.

13.2.1 (1) Transfusion # from TOP05

Record the corresponding transfusion number(s) from the TOP05, whether protocol driven or for clinical reasons.

13.2.2 (2) Adverse Event

In the space provided, select the adverse event you are reporting. Event(s) that are life threatening, result in death or classified as a Serious Adverse Event per ICH E3A (which may include mild, moderate or severe intensity and regardless of expectedness or attribution to study) should be recorded on this form. Please refer to the Toxicity Table in **Appendix E** for levels of intensity. All events that lead to death that occur between birth and 37 weeks PMA should be recorded on this form, regardless of transfusion history.

Adverse event recording will be limited to the following :

1. NEC (defined as Bell's Stage II or higher) at any time between birth and 37 weeks PMA
 - 1.a. Spontaneous intestinal perforation, without NEC, at any time between birth and 37 weeks PMA.

Note: The timing of SIP, or NEC-perforation or NEC of Stage II – will be taken from the time of the diagnostic Abdominal XR that leads the clinicians to diagnose this. The time of this will be recorded.

2. Respiratory deterioration up to 24 hours post-transfusion
3. Nosocomial sepsis, if this occurs up to 24 hours post-transfusion
 - All positive culture, blood stream infections

4. Hyperkalemia, if this occurs up to 24 hours post-transfusion
Must meet the capillary or arterial potassium value for each intensity grade AND if the K value is more than 0.5 mmol/L higher than pre-transfusion level.
5. Other
List any serious adverse event not otherwise pre-specified that, in the opinion of the investigator, has an unfavorable or unintended effect temporally associated with the infant's participation in research regardless of relationship to study or transfusion history (i.e., whether or not the infant ever received a transfusion. Also record all events that lead to death between birth and 37 weeks PMA.

13.2.3 (3) Onset Date, Time (4) Date Resolved

Date of onset is recorded as the first day that the clinical diagnosis is documented in the medical record, regardless of when it is discovered by the research team. Date resolved is when therapy for the diagnosis is discontinued or the clinical team is no longer monitoring the condition. If the event is ongoing at the end of status period code "1" rather than date resolved.

Onset time will be recorded for NEC and SIP. The timing of SIP, or NEC-perforation or NEC of Stage II – will be taken from the time of the diagnostic Abdominal XR that leads the clinicians to diagnose this. The time of this will be recorded.

13.2.4 (5) Relationship

Review the event with PI or attending Neonatologist to determine the likelihood that the event is attributable to study therapy and study procedures. Assign one of the following codes as appropriate to both columns.

- 0 = None** if there is no apparent potential relationship to the study therapy or procedures.
- 1 = Unlikely** if it is unlikely that there could be any relation to the study therapy or procedures.
- 2 = Possibly** if there is a possibility that the adverse event is related to the study therapy or procedures.
- 3 = Probably** if the adverse event is probably related to the study therapy or procedures.
- 4 = Definitely** if the adverse event clearly relates to the study therapy or procedures.

13.2.5 (6) Intensity Status

Review events with PI to best assign one of the following codes. See **Appendix E**.

- 1 = Mild**
- 2 = Moderate**
- 3 = Severe**
- 4 = Life Threatening***
- 5 = Death***

* Event(s) that are life threatening, result in death, or classified as a Serious Adverse Events per ICH E2A (which may include mild, moderate or severe intensity and regardless of expectedness)

or attribution to study) require notification to NICHD and RTI within one business day of discovery. The Medwatch (FDA Form 3500A) should be completed and faxed or emailed to: NICHD, Attn: Rosemary Higgins, M.D., (301) 496-3790 (higginsr@mail.nih.gov) and RTI, Attn: Meg Crawford (919) 485-7762 (NRNProtocolSupport@rti.org)

13.2.6 (7) Serious Status

Seriousness (not severity) is based on patient/event outcome or expected outcome and whether or not that poses a threat to a patient's life or functioning. For every adverse event that qualifies as serious code:

1= Results in death

2= Is life threatening

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe

3= Requires prolongation of hospitalization

4 = Results in persistent or significant disability/incapacity

5 = Other serious important medical events

This should be selected, when based on medical judgment, the event will require medical or surgical intervention to prevent a worse outcome.

6 = Not classified as serious

One additional category of "serious" that is listed in ICH E2A is a congenital anomaly/birth defect. This does not apply to patients in this study as they do not have potential to give birth during this study.

13.2.7 (8) Expectations

Many medical events, of all degrees of severity, occur among extremely preterm infants. Most are within the expected range of events that we expect, despite efforts to avoid them. Review events with PI to best assign one of the following codes to describe the expectation for this event.

1 = Expected A common event seen frequently among extremely premature infants, expected in half or more of infants.

2 = Unexpected This would be an event that you do not expect to see among premature infants, or an event that you do expect to see -- but not at the time during the infant's hospitalization that it actually occurs.

13.2.8 (9) Actions Taken

Record all action taken by clinical team in response to the diagnosis. Choose from the list provided:

1 = No change

2 = Supportive Rx

- 3 = Extensive Rx or Surgery
- 4 = Study procedures held
- 5 = Study procedures discontinued

13.2.9 (10) Final Outcome

Assign the appropriate status code below to describe the resolution of the event at the end of the study period in order for the form to be entered into the DMS as quickly as possible. If the outcome is ongoing when the form is initially completed, or if the outcome changes, the form can be modified at a later date.

- 1 = Completely resolved; no residual effects.
- 2 = Resolved with sequelae
- 3 = Patient died
- 4 = Ongoing

13.2.10 (11) Comments and PI Initials

This section is used for any comments that are relevant or helpful. Comments are not required. Additionally, the PI should use this column to acknowledge via initials that he/she has reviewed and agrees with information recorded for each adverse event. The initials will not be keyed into the DMS.

13.3 MedWatch Form

The MedWatch form is completed to further explain and give clinical specifics for all events that require prompt (faxed) reporting to RTI and NICHD as described in 13.1 above. The form will be completed with all pertinent information and signed by the PI or attending Neonatologist before it is faxed the RTI and NICHD. This form is not entered into the DMS. Do not include any HIPAA protected health information on this form or any attached clinical summaries, but rather identify the patient with their Network number and Study number. A fillable .pdf version of this form, with complete instructions for completion, is available on-line at:

<http://www.fda.gov/downloads/Safety/MedWatch/HowToReport/DownloadForms/UCM082728.p>.

CHAPTER 14. PROTOCOL VIOLATIONS AND MINOR DEVIATION FORM (TOP10)

14.1 Protocol Violations and Minor Deviations

Study implementation compliance will be monitored throughout the study. Deviations and violations from the protocol will be documented on the Protocol Deviation/Violation Form (TOP10). The purpose of this form is to facilitate the accurate documentation of the information and circumstances surrounding the protocol deviation/violation.

Distinguishing between the two is sometimes a matter of 'judgment'. Accordingly, please discuss with the site PI which category the episode falls under. In case of doubt, please do not hesitate to consult either Haresh Kirpalani or Ed Bell – or their delegates Aasma Chaudhary or Karen Johnson (Contacts are listed at the start of this MOP).

To assist in making the distinction we offer some examples that we believe may arise more frequently:

- i) A transfusion volume that is made in error (e.g., instead of 15 ml/kg, 30 ml/kg) that does not result in a significant clinical event for the infant with no sequelae is a minor deviation. If on the other hand a clinical deterioration is the result, this must be accompanied by a report of the adverse event toxicity table, and if needed a fuller brief narrative description.
- ii) A delay between the report back of a hemoglobin and a transfusion that is given at beyond the 12 hour specified window – is considered a minor deviation.
- iii) A delay between the report back of a hemoglobin and a triggered transfusion that is omitted – is considered a protocol violation.
- iv) A transfusion that is given as within the protocol pre-specified allowable 'clinical' guidelines, is not considered either a protocol violation or deviation. Please see chapter 9, section 9.2.1 on how to answer question 8 on the TOP05 form.
- v) A transfusion for an infant that is not algorithm driven, but where the infant is not septic, pre-operative, bleeding, receiving an exchange transfusion, severe hypotension, severe hypoxemia **with sustained FiO2 >90% despite optimization of ventilation** or in shock – is considered a protocol violation.
- vi) A transfusion that is not at or below the threshold-trigger value of hemoglobin/hematocrit is not permitted but if within 1 decimal point can be considered as a deviation rather than a violation.

14.2 Protocol Violation and Minor Deviation Form – TOP10

This form should be completed for all randomized patients whenever a protocol violation/deviation is encountered. This form also serves as confirmation of final protocol violation/deviation documentation. This form should be entered into the DMS. If more than one violation occurs on the same day, you can use one form. If violations occur on different days, use a separate form.

14.2.1 Section A. Occurrence of Protocol Violation/Deviation Events During Study Intervention (record Section B once per infant case)

1. Did any protocol violations or deviations occur for this infant?

Record 'Y' if any protocol violations or deviations occurred for this infant reportable by study staff. If yes, record first event(s) on the remaining form and use additional forms if other violations and deviations occur on other dates. This question only needs to be answered on the first form.

14.2.2 Section B. Event

1. Date of Event:

All dates for this study are recorded using the MM/DD/YYYY format.

2. Type of Event - Code the type of event:

1 = Protocol Violation: A deviation from the IRB approved protocol that may affect the subject's rights, safety, or well-being .

Examples include: administering a blood transfusion that does not meet a trigger and is not one of the clinical exemptions such as (1) pre-op; (2) bleeding; (3) severely ill and hypoxemic and/or (4) exchange transfusion. Any transfusion that is given outside of these parameters is considered a protocol violation.

Please refer to section 14.1 for more examples.

2 = Minor Protocol Deviation: A deviation from the IRB approved protocol that DOES NOT have a major impact on the subject's rights, safety or well-being, or the completeness, accuracy and reliability of the study data.

Examples include: transfusion is administered after 12 hours since the receipt of hemoglobin/hematocrit values.

Please refer to section 14.1 for more examples.

14.2.3 Section C. Protocol Violation/Deviation Details

Please answer yes or no to the following violations/deviations:

1. Ineligible infant randomized?

2. Lack of consent?

3. Infant randomized to wrong birth weight strata?

4. Infant not transfused per protocol?

If yes, select circumstance, enter transfusion # from the TOP05 form (if applicable) and provide additional details in Section D.

- Transfused > 12 hours after threshold reached
- Threshold met; no transfusion given
Examples include: decision made to withhold or withdraw care; clinical decision to not transfuse; parent requested not to transfuse. Please describe these circumstances in Section D.
- Transfusion skipped, no IV access

- Infant transfused, clinician preference
Examples include: Infant transfused prior to threshold due to change in medical status or because of no change in medical status, prompting a transfusion. Please describe these circumstances in Section D.
- Volume of transfusion in correct
- Other
Please specify violation and describe circumstances in Section D.

5. Other violation? (please describe)

14.2.4 Section D. Event Circumstances

1. Circumstances of the Protocol Violation/Deviation:

Please describe the circumstances that led to the protocol violation or deviation briefly, but in adequate detail to enable the circumstances to be understood. If there were medical reasons for deviating from the protocol, describe them.

2. Additional Comments

Enter any additional comments about the event here.

3. Name of Person who reported the protocol violation

Anyone can discover the deviation, please enter the name of the person reporting its discovery (for future reference if it is necessary).

4. Initials of person completing this form.

Record the initials of the person completing the form.

CHAPTER 15. STUDY WITHDRAWAL FORM (TOP11)

15.1 Study Withdrawal Form (TOP11)

Complete this form when a randomized infant has been withdrawn from study participation.

15.1.1 Section A. Withdrawal

1. Date infant withdrawn

Record the documented date the infant has been withdrawn from study. Withdrawal is a process and this date should reflect the date study diet or study-specific assessments have been halted or the date no further data can be obtained.

2. Select the withdraw status appropriate for this child:

Select the appropriate status for withdrawal

Withdrawn from study with permissions to continue data collection per protocol (i.e. no additional study-specific assessments will be completed but data collected as part of standard clinical practice may be used for study purposes)

Withdrawn from study with discontinuation of further data collection (i.e. no further data to be reported about this infant for this study)

3. Infant withdrawn by:

Use the following codes to identify who withdrew consent:

- 1 = Parent(s) or Legal Guardian(s)
- 2 = Physician
- 3 = Other (specify)

4. Reason(s) infant was withdrawn

Select the reason(s) the infant was withdrawn (select all that apply):

Infant too medically unstable to continue study participation

Reason not requested (specify below)

Reason not stated (specify below)

Other (specify below)

15.2.2 Section B. Additional Comments

1. Comments

Use this space for additional comments

2. Name of Person Obtaining Withdrawal

Record the name of person who obtained the withdrawal of consent.

Appendix A: Sample Consent

Parental Permission Form and HIPAA Authorization

Protocol Title: Transfusion of Prematures – Does a Liberal Red Blood Cell Transfusion Strategy Improve Neurologically-Intact Survival of Extremely-Low-Birth Weight Infants as Compared to a Restrictive Strategy

Transfusion of Prematures (TOP)

Short Title:

Principal Investigators: Haresh Kirpalani, BM, MSc (CHOP) 215-300-9475
Barbara Schmidt, MD (HUP) 215-662-3228
Soraya Abbasi, MD (PAH) 215-829-3301
Address written communications to either
i) NICU Division, Hospital University of Pennsylvania
Ravdin Building 8th floor
3400 Spruce Street
Philadelphia, PA 19104
Or
ii) NICU Division Pennsylvania Hospital
2nd floor Cathcart
800 Spruce Street
Philadelphia, PA 19107

Emergency Contact: Neonatology Attending on-call for HUP/CHOP
(215) 300-9475

PAH Intensive Care Nursery: 215-829-5070

Thank you for taking time to read this when so much is happening to your baby. We know it is a difficult time for you. This study is being performed at three sites of the CHOP Neonatology Division: (1) Hospital of the University of Pennsylvania Intensive Care Nursery; (2) Pennsylvania Hospital of the University of Pennsylvania Intensive Care Unit and, (3) Children's Hospital of the Philadelphia.

Why am I being asked to have my baby participate in the study?

You and your baby are being invited to participate in a research study. Your baby's participation is voluntary, which means that you can choose whether or not you want your baby to participate. If you choose not to have your baby participate, your baby will continue to get the best possible care.

Before you can make your decision, you will need to know what the study is about and the possible risks and benefits of being in this study. The research team is going to talk to you about the research study, and they will give you this consent form to read. You can also discuss it with your family, friends, or family doctor. You may find some of the medical language difficult to understand. Please ask the study doctor and/or the research team about this form. If you decide to have your baby participate, you will be asked to sign this form. This study is about hemoglobin – which is carried in red cells to transport oxygen to all of our tissues.

What is the purpose of this research study?

Babies who are born between 22 weeks and 0 days and 28 weeks and 6 days gestational age with a birth weight of less than or equal to 1000 gram are eligible for this study.

Very premature babies are at higher risk for death or survival with disabilities than infants born at full term. Their hospital care is very complex and may include multiple interventions. Many of these aspects of care, including the best blood levels to maintain, have not yet been established. Very premature babies frequently become anemic (or have a low hemoglobin) and often require blood transfusion. Most babies like yours receive at least one blood transfusion during their stay in the intensive care unit.

The purpose of this study is to compare two hemoglobin thresholds for deciding when to give blood transfusions to very premature babies. This study is trying to provide an answer to the question: "Is a higher hemoglobin threshold better than a lower hemoglobin threshold for transfusing babies?" Blood contains red cells, which carry hemoglobin. Hemoglobin is essential for life as it carries oxygen around the body. Hemoglobin can be measured, and is used by doctors as a measure of red blood cells in your baby's body. Hematocrit is another measure of red blood cells. When the hemoglobin or hematocrit falls below a certain level, doctors will transfuse the baby.

Some doctors tend to use a higher level of hemoglobin/hematocrit threshold and some doctors tend to use a lower level of hemoglobin/hematocrit threshold when making

this decision. The reason for this is that we do not know which level of hemoglobin/hematocrit threshold is better.

This study aims to help us find out when we should best transfuse babies by having some babies get transfused at high hemoglobin/hematocrit levels and others transfused at lower hemoglobin/hematocrit levels, and then comparing how many babies survive to be discharged home, and how many of those are doing well when they are 22 – 26 months old.

The levels at which babies are being transfused in this study are within the “normal” range at which doctors across the country routinely transfuse now, we are just establishing what is the best level.

This study has been approved and funded by the National Heart, Blood and Lung Institute (NHLBI), a branch of the National Institutes of Health and 18 large hospitals in the US are doing this study.

A description of this clinical trial is available on <http://www.ClinicalTrials.gov> (identification number NCT01702805, as required by U.S. Law. This Web site will not include information that can identify your baby. At most, the Web site will include a summary of the results. You can search this Web site at any time.

How long will my baby be in the study? How many babies will take part in the study?

Your baby will remain in the study for the duration of his/her hospital admission and until the date of the 22-26 month follow-up appointment. The randomization to the lower or higher hemoglobin threshold will only apply to the ICN admission. If you are unable to come to any of the CHOP affiliated Neonatal Follow-up clinics, we will help you to find an alternative Follow-up clinic.

About 1824 babies will take part in this study from 18 different university affiliated hospitals across the country. Approximately 500 babies will participate in this study at the CHOP neonatology sites.

What does the study involve?

Typically the decision to transfuse is based on many factors of which two are most important and common: how old baby is and whether baby needs help with breathing. In

this study, the decision about transfusion will be made at specified time points based on hemoglobin levels.

If you agree to this study, your baby will be randomly assigned, like the flip of a coin, to either the higher level of hemoglobin/hematocrit or the lower level. Both of these levels are within the usual range used by doctors in the NICU. Randomization means the decision when to transfuse is no longer done by your infant's doctor and is now done in accordance with the protocol.

If your baby were to get unexpectedly ill or have an unexpected urgent need for blood transfusion (where all doctors routinely give blood), your baby would get such a transfusion. Babies can receive blood transfusions outside of their study guidelines, if baby's doctors find there is an unexpected urgent need for a blood transfusion. Once baby has stabilized, future blood transfusion needs will be determined by the randomization arm.

We will ask you to complete an optional economic questionnaire that will help provide us with information as to how families cope with having a baby in the intensive care nursery, which will include additional expenses that you have related to your child's hospitalization and medical care following discharge.

We will also collect information from the hospital (not from you) about daily financial charges for your child's medical care. This will not include any of your personal financial information or your social security number. This will help us determine the cost of taking care of premature babies today in the United States.

You are free to decline to answer some or all of these questions. If you decide that you do not want to complete the economic questionnaire, this will not affect study participation

We will arrange for your baby to come back for a 22 month follow-up appointment. All extremely premature babies are routinely seen in the follow-up clinic to check how well they develop and grow. At this visit, we will perform a physical test to measure vision and hearing. Your baby will have routine developmental testing at this visit.

We will also observe how well your child has learned to walk, talk and play. We will also ask you to complete a short questionnaire about how your life and work has been impacted by your baby's stay in the hospital.

All parts of your baby's care will be the standard care for premature babies in the NICU, except for use of hemoglobin/hematocrit level to decide on transfusion, and the 2 questionnaires.

There are two periods in this study: (1) Hospital stay and (2) after your baby is discharged from the hospital.

The following chart is a summary of what will happen and when:

	1) Hospital Stay	2) After Discharge
Definition of the two periods	From birth to 36 weeks Postmenstrual age (or when you would have been 36 weeks in your pregnancy this is abbreviated as PMA)	Once your baby is discharged from the hospital, we will ask that you come for a follow-up visit at 22-26 months of age
What Happens at both of these periods?	Your baby will receive blood transfusions as needed, based on the hemoglobin/hematocrit threshold for their randomized group.	We will do a regular medical exam and measurements similar to a well-baby checkup.
What data is being collected?	We will record weight, head circumference weekly, head ultrasound results, laboratory results and any medical problems that occur during your baby's hospitalization.	We will perform special tests to assess your child's development, including questions about your baby's new milestones your baby since the last visit, (examples: sitting, crawling, holding toys, and talking). The study staff will also play with your child to determine motor and social skills.
When does the period end?	This phase ends when baby is discharged from the hospital or when the baby is 36 weeks PMA), whichever happens first.	We will have you complete a questionnaire about home and family at the follow-up visit. The study is over once this follow-up visit has been completed.

Follow up Visit

We will arrange for your baby to come back for a 22 month follow-up appointment. All extremely premature babies are routinely seen in the Follow-up clinic to check how well they develop and grow with a physical exam. At this visit, we will perform a simple test to measure vision and hearing.

We will also observe how well your child has learnt to walk, talk and play. The name of this evaluation is called Bayley Scale of Infant Development. We will also ask you to complete a short economic questionnaire about how your life and work has been impacted by your baby's stay in the hospital. This is similar to the questionnaire you may have completed while your baby was in the hospital, if completed previously and you are free to decline to answer some or all of these questions.

What are the possible risks or discomforts?

Your baby has been born very early, and is at risk for complications of extreme prematurity, and some of these babies die. This study is not altering standard of care. The risks associated with this study are similar to the risks that exist in current medical practice. Previous studies suggest that either too low or too high a hemoglobin could both have effects on the long term outcomes. A summary of these effects is provided in the table below.

Too low hemoglobin	Too high hemoglobin
▪ Too low hemoglobin may make it more difficult to give oxygen to the tissues	▪ Increased transfusion may increase iron, which may be linked to chronic lung disease (also known as BPD), or eye problems (retinopathy of prematurity),
▪ May cause necrotizing enterocolitis (a serious bowel infection)	▪ May cause necrotizing enterocolitis (a serious bowel infection)
▪ May contribute to increased apneas	▪ May take longer for baby's own blood system to produce blood by itself
• Weight gain may be slower	▪ May require more intra-venous lines in order to give blood transfusion

There are no extra blood tests being done on your baby for this study.

The overall risks associated with this study are the same risks that exist in current medical practice and in blood transfusion therapy. As for all non-study and clinical

blood transfusions, we will ask you to sign a separate consent form for blood transfusions that list possible risks of any transfusion including: infection, volume overload, transfusion reactions.

There is a chance that rate of death, bowel infections (Necrotizing Enterocolitis) and rate of disabilities among survivors will be very similar for infants in both groups. There is also a chance that either the high or low hemoglobin/hematocrit group could have higher or lower mortality rates, and higher or lower disability rates, or higher or lower rates of Necrotizing Enterocolitis.

Regardless of which group your baby is in, if your baby needs blood for emergency reasons, where all doctors would routinely give blood, your baby will get a transfusion. After the urgent need is over, your baby would return to the study protocol.

You may not be comfortable answering some of the questions in the questionnaire. If that is the case, please skip that question and go on. Skipping questions will not affect the care your baby receives in the NICU. All information you provide to the study team will be kept strictly confidential.

There may be other risks to the study that we don't know about now. If we found any new risks during the time your baby was in the study, we would let you know.

What if new information becomes available about the study?

During the course of this study, we may find more information that could be important to you. This includes information that, once learned, might cause you to change your mind about being in the study. We will notify you as soon as possible if such information becomes available.

What are the possible benefits of the study?

This study may not directly benefit your baby, although one group may have a lower rate of death or less disability at follow up than the other. We hope that, in the future, other people might benefit from this study because the knowledge learned may someday help guide transfusion decisions for premature babies.

What other choices does my baby have if I do not give permission for my baby to participate?

If you choose not to allow your baby to participate in this study and your baby needs a blood transfusion, the doctor will decide when to transfuse your baby as would normally occur in clinical care. The alternative to enrolling your child in this study is not to participate.

Will I be paid for being in this study?

You will not receive any payments for taking part in this study. However, if necessary at that time your travel costs are a problem, we will cover the cost of travel to the CHOP follow up clinic for the visit at 22 to 26 months.

Will I have to pay for anything?

While you are in this study, the cost of your baby's medical care – the blood transfusions, follow-up visit, medications and doctor visits – will continue to be billed to you or your insurance as these costs are associated with routine medical care. There is no cost associated with being in the study.

What happens if I am injured from being in the study?

If your baby gets hurt or gets sick from something that was done as part of this study, doctors at the clinic or hospital will arrange for any needed emergency medical care. The Hospital does not offer financial compensation or payment for injuries due to participation in this research. No funds have been set aside to compensate you in the event of injury.

You and your insurance company will be billed for the costs of any care or injuries.

If you think you or your baby have been injured from taking part in this study, call Dr. Haresh Kirpalani at 215-590-3730. He can go over things with you, let you know of resources that may be available and give you information on what you need to do.

In case of injury to your baby resulting from this study, you will not lose any legal rights by signing this form.

When is the Study over? Can I leave the Study before it ends?

This study is expected to end after all participants have completed their 22 - 26 month neurodevelopmental assessment visits, and all information has been collected. This study may also be stopped at any time by your physician, the study Sponsor, or the Food and Drug Administration (FDA) without your consent because:

- The Primary Investigator feels it is necessary for your child's health or safety. Such an action would not require your consent, but you will be informed if such a decision is made and the reason for this decision.
- The Sponsor, the study Principal Investigator, or the Food and Drug Administration (FDA) has decided to stop the study.

If you decide to participate, you are free to leave the study at anytime. Withdrawal will not interfere with your baby's future care.

Confidentiality

Every effort will be made to keep your baby's medical records confidential (secret). Only people involved with the study and other authorized persons will have access to the data and the baby's medical records.

We will do our best to make sure that the personal information obtained during the course of this research study will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Your baby will be assigned a unique study ID number. There will be one Master List which will contain the name of your baby and the assigned study ID number. No one outside of the immediate study team will know the true identity of your baby. Once your baby has completed the 22 month follow-up visit, the link between the name and study ID number will be destroyed. Only the study ID number is used on all study data forms.

HIPPA AUTHORIZATION SECTION

How will my personal information be protected?

This section gives more detailed information concerning how your baby's personal health information may be used and disclosed by the University of Pennsylvania Health Systems (UPHS), the School of Medicine and the individual Principal Investigator, subject to University of Pennsylvania procedures.

What personal health information is collected and used in this study and might be disclosed?

The following personal health information will be collected and used for research, and may be disclosed during your involvement with this research study:

- Name, address, telephone number date of birth, parental email addresses (if available)

- Personal and family medical history
- Current and past medications or therapies
- Information from a physical examination that generally also includes blood pressure values, heart rate, and temperature
- Results of tests your baby will undergo as described in the informed consent form.

Why is your personal contact and health information being used?

Your contact information is important for the research study to contact you during the study. Your baby's personal health information and results of tests and procedures are being collected as part of this research to conduct the research, oversee the research, and ensure the research was done correctly. In some situations your baby's personal health information might be used to help guide your medical treatment.

Which of our personnel may use or disclose your baby's personal health information?

- The Principal Investigator
- A member of the IRB or ethics committee that has approved the study
- Researchers working on this study from the Hospital University Pennsylvania or the Children's Hospital of Philadelphia
- The Follow-Up Clinics affiliated with the Hospital of University of Pennsylvania or Children's Hospital of Philadelphia

Who Outside of UPHS and the School of Medicine might receive your baby's personal health information?

As part of the study the Principal Investigator, the study team and others listed above, may disclose your baby's personal health information, including the results of the research study and procedures in addition to your personal contact information. This information may be disclosed to the those listed below:

Individuals or organizations responsible for administering the study:

- Dr Haresh Kirpalani and members of his research team at UPHS
- National Heart, Lung and Blood Institutes (Part of the NIH)

- The National Institute Child Health and Development (NICHD)
- Others: Hospital of University of Pennsylvania, Pennsylvania hospital or Children's Hospital of Philadelphia: Who may disclose your baby's personal health care information from this clinical trial to your baby's referring hospital-institution in order to better manage your baby's care; and the follow-up clinics may disclose information to your baby's primary care physician.

Regulatory and safety oversight organization

- The Office of Human Research protections
- The Study Data and Safety Monitoring Board

Once your baby's personal health information is disclosed to others outside of UPHS or the School of medicine, it may no longer be covered by federal privacy protection regulations. The Principal Investigator or study staff will inform you if there are any additions to the list above during your baby's active participation in the trial. Any additions will be subject to University of Pennsylvania procedures developed to protect your privacy.

How long may UPHS and the School of Medicine be able to use or disclose your baby's personal health information?

Your authorization of use of your baby's personal health informations for this specific study does not expire. Your baby's information may be held in a research database indefinitely. However UPHS and the School of Medicine may not re-use or re-disclose information collected in this study for a purpose other than this study unless:

- You have given written authorization to do so
- The University of Pennsylvania's Institutional review board grant permission after ensuring that appropriate privacy safeguards are in place
- As permitted by law

Electronic Medical Records and Research Results

What is an Electronic Medical Record?

An Electronic Medical Record (EMR) is an electronic version of the record of your baby's care within a health system. An EMR is simply a computerized version of a paper medical record. Your baby will have an EMR since he/she is an inpatient in the Intensive Care Nursery of the University of Pennsylvania Health System.

If you choose to have your baby participate in this trial, documentation of this will be included in the EMR. This trial does not require any additional tests or procedures outside of routine intensive care.

Documentation that is entered in the EMR, is accessible to appropriate UPHS workforce members that are not part of the research team. Information within your EMR may also be shared with others who are determined by UPHS to be appropriate to have access to your EMR (e.g. health insurance company, disability provider, etc).

Who can I call with questions, complaints or if I'm concerned about my baby's rights as a research subject?

If you have questions, concerns or complaints regarding your baby's participation in this research study or if you have any questions about your baby's rights as a research subject, you should speak with Dr. Haresh Kirpalani listed on page one of this form. If a member of the research team cannot be reached or you want to talk to someone other than those working on the study, you may contact the Office of Regulatory Affairs with any question, concerns or complaints at the University of Pennsylvania by calling (215) 898-2614.

Can you change your mind?

Yes, at any time you may withdraw your approval to allow the use and disclosure of your baby's personal health information as described above. You must do so in writing to the Principal Investigator at the address on the first page. Even if you withdraw your permission, your baby's personal health information that was collected before we received your written request may still be used and disclosed, as necessary for the study. If you withdraw your permission to use your baby's personal health information, your baby will also be withdrawn from the research study.

Parental Permission

When you sign this form, you are agreeing to allow your child to take part in this research study. This means that you have read the consent form, your questions have been answered, and you have decided to allow your baby to be enrolled. Your signature also means that you are permitting the University of Pennsylvania to use your child's personal health information collected about you for research purposes within our institution. You are also allowing the University of Pennsylvania to disclose that personal health information to outside organizations or people involved with the operations of this study.

You will be given a copy of this Parental Informed Consent and HIPPA Authorization form describing your and your baby's confidentiality and privacy rights.

Name of Subject (Please Print)

Name of Person Obtaining
Consent (Please Print)

Signature

Date

For subjects unable to give authorization, the authorization is given by the following authorized subject representative:

Authorized parent or

Parent or Legal Guardian

Date

Legal guardian **[print]**

representative Signature

Provide a brief description of above person authority to serve as the subject's authorized representative.

Appendix B: Randomization Script

The telephone randomization system can be accessed by dialing 1-800-262-2673.

If problems are encountered during the process, contact RTI at 1-866-253-1624.

DCC Script:	<i>Hello, this is the NICHD Neonatal Network Randomization System. Please enter your 4-digit password now:</i>			
Caller:	Enter your password:			
DCC Script	<i>You have entered the following password (xxxx); if correct, press 1, to enter the value again, press 2.</i>			
Caller:	Press	1	to proceed with the randomization	
DCC Script:	<i>Has parental consent been obtained for this infant? If Yes, please press 1 to proceed with the randomization. If No, please hang up and call back after consent has been obtained.</i>			
Caller:	Press	1	to proceed with the randomization.	
DCC Script:	<i>Press 5 for the TOP protocol.</i>			
Caller:	Press	5	to enter the TOP protocol.	
DCC Script:	<i>Is this randomization for the TOP Protocol? If Yes, press 1, if No please hang up and call back to get the correct protocol.</i>			
Caller:	Press	1	to continue in the TOP Protocol.	
DCC Script	<i>Please enter the first and last initials of your name:</i>			
Caller:	Enter your initials:			
DCC Script:	<i>Is this a new randomization or an existing randomization? If this is a new TOP randomization, press 1, if this is existing verification of an old randomization press 2.</i>			
Caller:	Press	1	if this is a new randomization.	
Caller:	Press	2	to hear a previous randomization assignment restated.	
DCC script	<i>Please enter the four digit birth weight for this infant in grams.</i>			
Caller	Press			
DCC Script	<i>The birth weight you have entered is (system repeats birth weight) If this is correct, press 1, press 2 to enter the correct birth weight.</i>			
Caller	Press	1	if this birth weight is correct	
Caller	Press	2	to enter the birth weight	
DCC script	<i>Please enter the four digit Study Number for the Infant.</i>			
Caller	Enter the Study Number T			
DCC script	<i>The study number you have entered is (system repeats study number) If this is correct, press 1. Press 2 to enter the correct study number.</i>			
Caller:	Press	1	if this number is correct	
Caller:	Press	2	to enter the correct study number	
DCC script	<i>You have been assigned the following randomization number: _____. To continue, press 1. To have the randomization number repeated, press 2.</i>			
Caller:	Press	1	to continue	
Caller:	Press	2	To hear the randomization number again	
DCC script	<i>The treatment assignment is {High OR Low Threshold}. Press 1 to continue. Press 2 to listen again.</i>			
Caller:	Press	1	to confirm that you have received this assignment and conclude the session.	
Caller:	Press	2	To hear the assignment restated.	
DCC Script:	<i>The randomization session has concluded. Thank you and goodbye.</i>			

Appendix C: Randomization Tracking

Patient's Name Last , First	Hospital Number	Randomization Number	Treatment Assignment*	Randomization Date (mm/dd/yyyy)	Study No.
		_____	☐ High Threshold ☐ Low Threshold	___/___/_____	T_____
		_____	☐ High Threshold ☐ Low Threshold	___/___/_____	T_____
		_____	☐ High Threshold ☐ Low Threshold	___/___/_____	T_____
		_____	☐ High Threshold ☐ Low Threshold	___/___/_____	T_____
		_____	☐ High Threshold ☐ Low Threshold	___/___/_____	T_____
		_____	☐ High Threshold ☐ Low Threshold	___/___/_____	T_____
		_____	☐ High Threshold ☐ Low Threshold	___/___/_____	T_____
		_____	☐ High Threshold ☐ Low Threshold	___/___/_____	T_____
		_____	☐ High Threshold ☐ Low Threshold	___/___/_____	T_____
		_____	☐ High Threshold ☐ Low Threshold	___/___/_____	T_____
		_____	☐ High Threshold ☐ Low Threshold	___/___/_____	T_____
		_____	☐ High Threshold ☐ Low Threshold	___/___/_____	T_____

Appendix D: SNAP Score Article

Appendix E: Toxicity Table

This Toxicity Table is to assist with evaluation of intensity and seriousness of specific adverse events that are outlined in the protocol, any event that leads to death and other events that could be classified as a Serious, Unexpected Adverse Drug Reaction (ADR) per ICH E2A. Expected morbidities of prematurity which are captured in the Neonatal Research Network Generic Data Base or elsewhere in the data set for this study are not addressed.

Event	INTENSITY			SERIOUSNESS	
	Grade I Mild	Grade II Moderate	Grade III Severe	Life Threatening	Death from Event
NEC					
Necrotizing Enterocolitis at any time between birth and 37 weeks PMA)	Bell's Stage I: temp instability, apnea, bradycardia, lethargy, distension, feeding intolerance, ileus, bloody stool	Bell's Stage II: Stage I + pneumatosis, mild metabolic acidosis or thrombocytopenia, abdominal tenderness or cellulitis	Bell's Criteria III A all previous + hypotension, severe apnea or acidosis, DIC, neutropenia, peritonitis, ascites	Bell's Criteria III B All previous + pneumoperitoneum/bowel perforation	Demise associated with NEC
SIP					
Spontaneous intestinal perforation, without NEC, at any time between birth and 37 weeks PMA	Abdominal distension	Gastric residuals, absent stooling, NO pneumatosis Bluish discoloration of the abdomen with minimal prodromal symptoms	Intestinal perforation/free air without pneumatosis or bowel necrosis	Intestinal perforation/free air; systemic symptoms including but not limited to tachycardia, hypotension, shock, respiratory deterioration	Demise associated with SIP
RESPIRATORY					
Respiratory Deterioration (up to 24 hours post transfusion)	New or increased severity of apnea or desaturations	Hypoxia, hypercarbia, acidosis or increased work of breathing requiring increased $\text{FiO}_2 > 10\%$ or increase in MAP by 2 cmH ₂ O from baseline, any mode change demanding an escalation in respiratory support (e.g., RA to NC, CPAP, or Nasal SIMV ; from non-intubated respiratory support to intubated support)	Hypoxia, hypercarbia, acidosis or increased work of breathing requiring increased mode of support to HFOV, HFJV and initiation of iNO therapy	ECMO	Demise from respiratory failure
INFECTION					
Nosocomial sepsis (up to 24 hours post transfusion)	Positive blood culture considered contaminant and not treated	Positive blood culture treated for ≤ 5 days	Blood culture positive for bacteria, virus or fungus treated for ≥ 5 days	Blood culture positive for bacteria, virus or fungus treated for ≥ 5 days + requiring significant respiratory support or extensive medical treatment	Demise from culture positive septicemia

METABOLIC

Hyperkalemia (up to 24 hours post transfusion)

Capillary potassium value = 6-<7mmol/L or Venous or arterial potassium value = 5-<6 mmol/L, and more than 0.5 mmol/L higher than pre-transfusion level

Capillary potassium value = 7-<8 mmol/L or Venous or arterial potassium value =6-<7mmol/L, and more than 0.5 mmol/L higher than pre-transfusion level

Potassium ≥ 8.0 mmol/L or requiring intense medical therapy or dialysis

Demise with hyperkalemia

OTHER

Events not listed, including any event leading to death

Mild transient symptoms, which are unexpected and not collected elsewhere in the data, requiring only **monitoring or symptomatic treatment**

Moderate illness or condition, which is unexpected and not collected elsewhere, with new or significantly altered treatment

Severe illness or condition, which is unexpected and not collected, **which is unresponsive to medical treatment**

Life threatening, unexpected illness or condition requiring major surgery, significant respiratory support or extensive medical treatment

Any event leading to death