Informed Consent Form

Project Title: 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?

Section A: The nature, duration and purpose of study

You are being asked to allow your child to participate in a research study which is sponsored by the National Institute of Child Health and Human Development (NICHD) and the National Heart, Lung and Blood Institute (NHLBI), branches of the National Institutes of Health. This research study includes premature infants born less than 29 weeks' gestation with birth weights less than or equal to 1000 grams.

Premature infants require many blood tests while in the Neonatal Intensive Care Unit to monitor their condition. One important test, a complete blood count (CBC), measures the hematocrit which is the number of red blood cells in the blood. The red blood cells are important because they carry oxygen throughout the body. The body produces red blood cells in the bone marrow (inside of the bones). Premature infants may become anemic (low hematocrit due to decreased number of red blood cells) because they cannot produce replacement red blood cells as quickly as is needed to keep their blood counts within the normal range. In these infants a blood transfusion can be given to help increase the red blood cell count to a normal range.

Doctors monitor complete blood counts as often as they feel it is necessary. If the hematocrit falls below a certain level, the infant will be given a red blood cell transfusion to increase the hematocrit. However, some doctors use a higher hematocrit level and some doctors use a lower hematocrit level to decide when to give a red blood cell transfusion because it is not known at which hematocrit level premature infants should receive a transfusion.

The purpose of this research study is to gather information to find out which hematocrit level should be used to transfuse red blood cells for the best results in premature infants. This study will be conducted at 18 large hospital centers in the US and will enroll 1824 infants from all the centers. A description of this clinical trial will be available on http: ***www.ClinicalTrials.gov***, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at anytime. The identifier number for this study is: NCT 01702805
Your child will remain in the study until your child is 22-26 months corrected age (time from his/her due date). Study participant's will be followed throughout their hospitalization and will

return to the Women & Infants Follow up Clinic at 22-26 months corrected age for follow up. You will be reimbursed $25 for this visit.

Section B: The means by which it is conducted
If you allow your child to participate in this study, your child will be randomly assigned (like a flip of a coin) to either the higher or lower hematocrit level. Both of these levels are in the usual range used by doctors in the NICU. The doctor will use this level of hematocrit to decide when to transfuse your child. If your child has a serious or unexpected event and requires a transfusion urgently your child's doctor will order a transfusion regardless of the hematocrit level at that time.

All of the blood tests that are done are routine standard of care. No extra blood tests will be done as part of this study. We will ask you to complete an economic questionnaire that will help provide us with information as to how families cope with having a baby in the intensive care nursery. This survey will ask about costs to you and your family while your child is in the hospital. If you feel uncomfortable answering any question, you may feel free to leave the question blank.

We will arrange for your baby to come back for a 22 month corrected age follow-up appointment. All extremely premature babies are routinely seen in the Follow-up clinic to check how well they develop and grow. We will also observe how well your child has learnt to walk, talk and play. These visits may take up to 1 ½ to 2 hours. 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. There are no added costs to you for having your baby participate in this study.

Section C: The possible benefit
There may be no benefit to your child from participating in this study. There may be benefit to your child if it turns out that either the higher hematocrit or lower hematocrit level show benefit. It is hoped that information gained from this study will help premature infants in the future. There is no benefit to you or your child for completing the cost of care survey.

Section D: The risks and discomforts.
If your child is assigned to the higher hematocrit level he/she may receive more blood transfusions, and if assigned to the lower hematocrit level may receive fewer transfusions. Both the higher hematocrit and lower hematocrit levels are within the range of hematocrit levels normally used in the NICU to determine when to give a red blood cell transfusion.

There is a risk of loss of confidentiality when completing the cost of care survey. Your survey will be identified by a study ID number and will not be shared with anyone outside of the study investigators.

A blood transfusion may result in changes in electrolytes (potassium or calcium) or sugar (glucose) levels in the blood. There is also a remote possibility of an infection or a reaction to the blood transfusion. However, strict guidelines for donor recruitment and blood screening and processing have decreased the risks associated with receiving a blood transfusion.

Chronic anemia may also be a risk for necrotizing enterocolitis (NEC), an infection of the intestines that can cause intestinal perforation. However, since there is no evidence of transfusions causing gut injury, the risks of receiving a red blood cell transfusion are no different when participating in this study as they are for usual care.

Section E: Alternatives

The only alternative is to not participate in this research study. Your choice will not affect the usual medical care your child will receive. Your child may receive one or more transfusions as part of his/her usual care.

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1. I have been told about this study. The experimental procedures have been explained to me. I have had a chance to ask questions. My questions were answered to my satisfaction.

2. I agree that my child and my confidential, protected health care information may be shared with people and groups associated with this study. My child and my confidential health care information will be used only as necessary to participate in this study. Except when required by law my child and I will not be identified in the study records disclosed outside this Hospital or participating institutions. For example, names, social security number, address, telephone number or any other direct personal identifier will not be shared. For records disclosed outside this Hospital or participating outside institutions, the investigator or his staff will assign my child a unique identifying code. The key to this code will be kept in a locked file in Dr. Abbot Laptook's office.

3. I agree that as part of the study that Dr. Abbot Laptook and his study team may report the results of study related laboratory tests, information about transfusions including vital signs, respiratory support before, during and after each transfusion, information about feedings, intake, output, growth measurements, medications, ultrasound and radiology imaging reports to the sponsor of the study the NICHD and the NHLBI and the Data Coordinating Center the Research Triangle Institute (RTI). No results will be released with my child or my identity. Information will also be collected from my child's doctor after discharge or in the event that my child is treated at a hospital other than Women & Infants Hospital prior to 22 corrected months of age.

   Information will only be released as required by law when reasonable cause is shown under government regulations, or proper judicial orders. It will also be released if requested to an official of the United States Food and Drug Administration, the United States Department of Health and Human Services, the United States Inspector General, the United States Office of Civil Rights, representatives of the NICHD, NHLBI and the Women & Infants Hospital and its Institutional Review Board as well as the Data Coordinating Center (RTI). If any of these groups review the research record, it may also need to review the entire medical record. If protected health care information is disclosed by the sponsor, it is no longer covered by the federal privacy regulations.

4. The principal investigator will keep the study records until the youngest subject in the study is 23 years. At that time, the research information not already in my child's medical record

will be destroyed or information identifying my child or I will be removed from such study records. Any research information in the medical record will be kept indefinitely.

5. Information from the study will be used for education or research purposes. No names or identifying information will be used.

6. I will be told of any changes to the risks or benefits of this study.

7. My child does not have to take part in this study.

   I do not have to allow use of my or my child's confidential, protected health information. My agreement to share my or my child's protected, personal health information will not expire until the completion and publication of the study.

8. I can withdraw my consent at anytime. My child and I may stop taking part in the study at any time. My child will still receive the best care possible. If I want to withdraw I will contact Dr. Abbot Laptook in writing and tell him I am withdrawing. His mailing address is Women & Infants Hospital, Pediatric Department, and 101 Dudley Street, Providence, RI 02905. If I withdraw my consent or permission the information which has already been collected about me and my child by the Hospital or the researchers will be kept by the researchers or hospital. This information may be needed to complete reports of this research.

9. If my child is injured as a result of this research, I will notify the Principal Investigator Dr. Abbot Laptook, at 401-274-1122 x 7421.

   If my child is injured in a research project, treatment will be provided at Women & Infants Hospital, or at another appropriate health care institution, at no cost to me beyond that which third party payers will cover.

   Further information in regard to this may be obtained from the Director of IRB Administration, who may be reached at (401)-453-7677.

10. If I have questions about this study, I may call Dr. Abbot Laptook, at 401-274-1122 x 7421. If I have questions about my rights as a research subject, I may call the Director of IRB Administration at (401) 453-7677.

11. My permission to allow the investigator and research staff to review my and my child's personal health information will end after completion and publication of this study.

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12. I will be given a copy of this signed consent form.

Future Contact: I have initialed below whether I authorize the researcher to contact me.

_____ I authorize the researchers to contact me in the future for research purposes

_____ I do not authorize the researchers to contact me in the future for research purposes

Name of Child_____

Signature: _____ Date: _____ Time: ___: ___ am/pm

Name (please print):_____

If not for self: relationship to patient: _____

Name of Translator (if used): _____

Translator's signature: _____

Person who explained study: _____Date: _____
Signature

_____
Printed name

Hospital policy states that the signed original consent form is to be included in the subject's medical record. One copy of the original signed consent form is to be given to the subject. One copy of the signed original consent form should be retained in the investigator's files.

UNIVERSITY HOSPITALS CASE MEDICAL CENTER
CONSENT FOR INVESTIGATIONAL STUDIES
(v. 07.2010)

Project Title: TRANSFUSION OF PREMATURES (TOP)– DOES A LIBERAL RED BLOOD CELL TRANSFUSION STRATEGY IMPROVE NEUROLOGICALLY-INTACT SURVIVAL OF EXTREMELY-LOW-BIRTH-WEIGHT INFANTS AS COMPARED TO A RESTRICTIVE STRATEGY

Principal Investigator: Michele Walsh, MD

Introduction
You are being asked to allow your child to participate in a research study which is sponsored by the National Institute of Child Health and Human Development (NICHD) and the National Heart, Lung and Blood Institute (NHLBI), branches of the National Institutes of Health. This research study includes premature infants born less than 29 weeks' gestation with birthweights less than or equal to 1000 grams.

Premature infants require many blood tests while in the neonatal intensive care to monitor their condition. One important test, a complete blood count (CBC), measures the hematocrit which is the number of red blood cells in the blood. The red blood cells are important because they carry oxygen throughout the body. The body produces red blood cells in the bone marrow (inside of the bones). Premature infants may become anemic (low hematocrit due to decreased number of red blood cells) because they cannot produce replacement red blood cells as quickly as is needed to keep their blood counts in the normal range. A blood transfusion can be given to help increase the red blood cell count to a normal range.

The doctors monitor complete blood counts weekly or more often, if they feel it is necessary. If the hematocrit falls below a certain level, the doctors will give a red blood cell transfusion to increase the hematocrit. However, some doctors use a higher hematocrit level and some doctors use a lower hematocrit level to decide when to give a red blood cell transfusion because it is not known at which hematocrit level premature infants should receive a transfusion.

Purpose
The purpose of this study is to find out which hematocrit level should be used when deciding to give a blood transfusion to premature infants. All study infants will receive usual care including blood transfusions, if needed, while in the hospital. After discharge, study infants will be evaluated for their growth and development at 22-26 months' corrected age (time from his/her due date).

A secondary purpose of this study will be to see if there cost differences between the two hematocrit level groups. Information about costs in the hospital and cost to you and your family while your child is hospitalized and after discharge will be evaluated.

A total of 1824 premature infants in 18 centers across the U.S. will participate in this study. Approximately 100 patients from Rainbow Babies and Children's Hospital will be enrolled in this study.

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Principal Investigator: Michele Walsh, MD

U.S NATIONAL INSTITUTES OF HEALTH (NIH) CLINICAL TRIALS DATABASE:
A description of this clinical trial is available on http://www.clinicaltrials.gov as required by U.S. Law. This website will not include information that can identify you. You can search this website at any time to find out information about the trial and basic results. This trial is registered under the number NCT01702805.

Study Procedures

We will discuss this study with you in the first 48 hours after your child's birth. If you allow your child to participate in this study, he/she will be randomized (chosen by chance like a toss of a coin) to a higher or lower hematocrit level to be used determine when he/she will receive a blood transfusion. Your child has an equal chance of being assigned to either the higher or lower hematocrit level.

The doctors will order complete blood counts according to usual NICU routines and also if they feel it is necessary for the care of your child. If your child has a hematocrit level that falls below his/her assigned level (higher hematocrit or lower hematocrit), a transfusion will be ordered by the clinical team. The study hematocrit levels are within the usual range of hematocrit levels used when deciding if infants require a transfusion.

If your child has a serious event or has an unexpected urgent need for a blood transfusion, your child's doctor may order a transfusion regardless of the hematocrit level.

We will collect information about your child during the time he/she is in the hospital. This will include results of complete blood counts, information about transfusions including vital signs, breathing support before, during and after each transfusion, and feedings and medications your child is receiving. We will also follow his/her growth and record results of head ultrasound tests that are performed. Information will be collected from your child's medical record prior to as well as after study enrollment, until the time he/she comes for a follow-up visit at 22-26 months' corrected age (time from his/her due date). We would like your permission to collect information from your child's doctor after discharge or in the event that your child is treated at a hospital other than Rainbow Babies and Children's Hospital.

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We will ask you to complete a short survey during your child's hospitalization. This survey will ask about costs of care to you and your family while your child is in the hospital. We will ask you to complete a second survey at the follow-up visit about cost to you and your family after your child's discharge from the hospital. Your responses will be identified by a study ID number and will remain confidential. If you feel uncomfortable answering any question, you may feel free to leave the question blank. Each survey will take about 45 minutes or less to complete.

Risks

The risks of receiving a red blood cell transfusion are no different when participating in this study as they are for usual care. A blood transfusion may result in changes electrolytes (potassium or calcium) or sugar (glucose) levels in the blood. There is also a remote possibility of an infection or a reaction to the blood transfusion. However, strict guidelines for donor recruitment and blood screening and processing have decreased the risks associated with receiving a blood transfusion. If your child is assigned to the higher hematocrit level he/she may receive more blood transfusions and if assigned to the lower hematocrit level may receive fewer transfusions. Both the higher hematocrit and lower hematocrit levels are within the range of hematocrit levels normally used in the NICU to determine when to give a red blood cell transfusion.

There is a risk of loss of confidentiality when completing the cost of care survey. Your survey will be identified by a study ID number and only be used by the study investigators.

Benefits

There may be no benefit to your child from participating in this study. There may be benefit to your child if it turns out that either the higher hematocrit or lower hematocrit level show benefit. It is hoped that information gained from this study will help premature infants in the future.

There is no benefit to you or your child for completing the cost of care survey.

Alternatives to Study Participation

The only alternative is to not participate in this research study. Your choice will not affect the usual medical care your child will receive.

Financial Information

There will be no cost to you or your insurance company for your child's participation in this study. You will not be paid for your child's participation in this study.

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All procedures and medications that are given as standard of care will be the responsibility of you and your insurance. This will include complete blood counts (CBC) and blood transfusions ordered by your child's doctor.

Research Related Injury

If injury occurs as a result of your child's involvement in this research, medical treatment is available from University Hospitals or another medical facility but your/your medical insurance will be responsible for the cost of this treatment. A research related injury is an injury that happens as a result of taking part in a research study. If you are injured by a medical treatment or procedure that you would have received even if you were not in the study, that is not considered a 'research injury.' There are no plans for payment of medical expenses or other payments. Including lost wages, for any research related injury. To help avoid injury, it is very important to follow all study directions.

Confidentiality

Information collected for this study will be sent electronically to a central data center via a dedicated, password sensitive computer. Your child will be identified by a study number and not by name or other identifying information.

If it is necessary for the study personnel to contact you or your child at a later time for follow-up, we will contact you at the address and/or telephone numbers you have provided. If we cannot locate you at the address or telephone numbers you have provided, we may use other information in the medical record such as social security numbers, your child's pediatrician or other contact information. We may contact you or your child until he/she reaches school age (6-7 years).

Privacy of Protected Health Information

The Health Insurance Portability & Accountability Act (HIPAA) is a Federal law that helps to protect the privacy of your child's health information and to whom this information may be shared within and outside of University Hospitals. This Authorization form is specifically for a research study entitled "TRANSFUSION OF PREMATURES (TOP)–DOES A LIBERAL RED BLOOD CELL TRANSFUSION STRATEGY IMPROVE NEUROLOGICALLY-INTACT SURVIVAL OF EXTREMELY-LOW-BIRTH-WEIGHT INFANTS AS COMPARED TO A RESTRICTIVE STRATEGY" and will tell you what health information (called Protected Health Information or PHI) will be collected for this research study, who will see your child's PHI and in what ways they can use the information. In order for the Principal Investigator, Dr. Michele Walsh and the research study staff to collect and use your child's PHI, you must sign this authorization form.

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You will receive a copy of this signed Authorization for your records. If you do not sign this form, your child may not join this study. Your decision to allow the use and disclosure of your child's PHI is voluntary and will have no impact on your child's treatment at University Hospitals. By signing this form, you are allowing the researchers for this study to use and disclose your child's PHI in the manner described below.
Generally the Principal Investigator and study staff at University Hospitals and Case Western Reserve University who are working on this research project will know that your child is in a research study and will see and use your child's PHI. The researchers working on this study will collect the following PHI about your child: information about your child while in the NICU including results of blood counts, information about blood transfusions, feedings and medications and his/her growth and development at 2 years of age. This PHI will be used to find out if higher or lower hematocrit levels for transfusion will result in improved outcomes at 2 years of age. Your access to your child's PHI may be limited during the study to protect the study results.

Your child's PHI may also be shared with the following groups/persons associated with this research study or involved in the review of research: National Institute of Child Health and Human Development, National Heart, Lung and Blood Institute, Research Triangle Institute, participating centers of the Neonatal Research Network, other staff from the Principal Investigator's medical practice group; University Hospitals, including the Center for Clinical Research and the Law Department; Government representatives or Federal agencies, when required by law.

Your permission to use and disclose your child's PHI does not expire. However, you have the right to change your mind at any time and revoke your authorization. If you revoke your authorization, the researchers will continue to use the information that they previously collected, but they will not collect any additional information. Also, if you revoke your authorization your child may no longer be able to participate in the research study. To revoke your permission, you must do so in writing by sending a letter to Dr. Michele Walsh, 11100 Euclid Avenue, Cleveland, OH 44106-6010. If you have a complaint or concerns about the privacy of your health information, you may also write to the UH Privacy Officer, Management Service Center, 3605 Warrensville Center, MSC 9105, Shaker Heights, OH 44122 or to the Federal Department of Health and Human Services (DHHS) at DHHS Regional Manager, Office of Civil Rights, US Department of Health and Human Services Government Center, JF Kennedy Federal Building, Room 1875, Boston, MA 02203. Complaints should be sent within 180 days of finding out about the problem.

The researchers and staff agree to protect your child's health information by using and disclosing it only as permitted by you in this Authorization and as directed by state and Federal law. University

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Hospitals is committed to protecting your child's confidentiality. Please understand that once your child's PHI has been disclosed to anyone outside of University Hospitals, there is a risk that your child's PHI may no longer be protected; however other Federal and State laws may provide continued protection of your child's information.

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Summary of your rights as a participant in a research study

Your child's participation in this research study is voluntary. Refusing to participate will not alter your child's usual health care or involve any penalty or loss of benefits to which your child is otherwise entitled. If you decide for your child to join the study, you may withdraw at any time and for any reason without penalty or loss of benefits. If information generated from this study is published or presented, your child's identity will not be revealed. In the event new information becomes available that may affect the risks or benefits associated with this study or your willingness for your child to participate in it, you will be notified so that you can decide whether or not to continue participating. If your child experiences physical injury or illness as a result of participating in this research study, medical care is available at University Hospitals Case Medical Center (UHCMC) or elsewhere; however, UHCMC has no plans to provide free care or compensation for lost wages.

Disclosure of your study records

Efforts will be made to keep the personal information in your child's research record private and confidential, but absolute confidentiality cannot be guaranteed. The University Hospitals Case Medical Center Institutional Review Board may review your child's study records. If this study is regulated by the Food and Drug Administration (FDA), there is a possibility that the FDA might inspect your child's records. In addition, for treatment studies, the study sponsor and possibly foreign regulatory agencies may also review your child's records. If your child's records are reviewed your child's identity could become known.

Contact information

_____ has described to you what is going to be done, the risks, hazards, and benefits involved. The Principal Investigator Dr. Michele Walsh can also be contacted at 216-844-3759. If you have any questions, concerns or complaints about the study in the future, you may also contact them later.

If the researchers cannot be reached, or if you would like to talk to someone other than the researcher(s) about; concerns regarding the study; research participant's rights; research- related injury; or other human subject issues, please call the University Hospitals Case Medical Center's Research Subject Rights phone line at (216) 983-4979 or write to: The Chief Medical Officer, The Center for Clinical Research, University Hospitals Case Medical Center, 11100 Euclid Avenue, Lakeside 1400, Cleveland, Ohio, 44106-7061.

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Signature

Signing below indicates that you have been informed about the research study in which you voluntarily agree for your child to participate; that you have asked any questions about the study that you may have; and that the information given to you has permitted you to make a fully informed and free decision about your child's participation in the study. By signing this consent form, you do not waive any legal rights, and the investigator(s) or sponsor(s) are not relieved of any liability they may have. A copy of this consent form will be provided to you.

X	
Name of Participant	
X	
Signature of Parent/Legal Guardian	Date
X	
Printed name of Parent/Legal Guardian	
X	
If Legal Guardian, indicate relationship to child	

X	
Signature of Witness	Date
X	
Printed Name of Witness	

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Principal Investigator: Michele Walsh, MD

X	
Signature of person obtaining informed consent	Date
X	
Printed name of person obtaining informed consent	
X	
Signature of Principal Investigator	Date
X	
Printed name of Principal Investigator	

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The purpose of this study is to find out which hematocrit level should be used when deciding to give a blood transfusion to premature infants. All study infants will receive usual care including blood transfusions, if needed, while in the hospital. After discharge, study infants will be evaluated for their growth and development at 22-26 months' corrected age (time from his/her due date).

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Principal Investigator: Michele Walsh, MD

U.S NATIONAL INSTITUTES OF HEALTH (NIH) CLINICAL TRIALS DATABASE:
A description of this clinical trial is available on http://www.clinicaltrials.gov as required by U.S. Law. This website will not include information that can identify you. You can search this website at any time to find out information about the trial and basic results. This trial is registered under the number NCT01702805.

Study Procedures

We will discuss this study with you in the first 48 hours after your child's birth. If you allow your child to participate in this study, he/she will be randomized (chosen by chance like a toss of a coin) to a higher or lower hematocrit level to be used determine when he/she will receive a blood transfusion. Your child has an equal chance of being assigned to either the higher or lower hematocrit level.

The doctors will order complete blood counts according to usual NICU routines and also if they feel it is necessary for the care of your child. If your child has a hematocrit level that falls below his/her assigned level (higher hematocrit or lower hematocrit), a transfusion will be ordered by the clinical team. The study hematocrit levels are within the usual range of hematocrit levels used when deciding if infants require a transfusion.

If your child has a serious event or has an unexpected urgent need for a blood transfusion, your child's doctor may order a transfusion regardless of the hematocrit level.

We will collect information about your child during the time he/she is in the hospital. This will include results of complete blood counts, information about transfusions including vital signs, breathing support before, during and after each transfusion, and feedings and medications your child is receiving. We will also follow his/her growth and record results of head ultrasound tests that are performed. Information will be collected from your child's medical record prior to as well as after study enrollment, until the time he/she comes for a follow-up visit at 22-26 months' corrected age (time from his/her due date). We would like your permission to collect information from your child's doctor after discharge or in the event that your child is treated at a hospital other than Rainbow Babies and Children's Hospital.

We will ask you to complete a short survey during your child's hospitalization. This survey will ask about costs of care to you and your family while your child is in the hospital. Your responses will be identified by a study ID number and will remain confidential. If you feel uncomfortable answering any question, you may feel free to leave the question blank. This survey will take about 45 minutes to complete.

UNIVERSITY HOSPITALS
CASE MEDICAL CENTER
CONSENT FOR INVESTIGATIONAL STUDIES
(v. 07.2010)

Project Title: TRANSFUSION OF PREMATURES (TOP)– DOES A LIBERAL RED BLOOD CELL TRANSFUSION STRATEGY IMPROVE NEUROLOGICALLY-INTACT SURVIVAL OF EXTREMELY-LOW-BIRTH-WEIGHT INFANTS AS COMPARED TO A RESTRICTIVE STRATEGY

Principal Investigator: Michele Walsh, MD

Risks

The risks of receiving a red blood cell transfusion are no different when participating in this study as they are for usual care. A blood transfusion may result in changes electrolytes (potassium or calcium) or sugar (glucose) levels in the blood. There is also a remote possibility of an infection or a reaction to the blood transfusion. However, strict guidelines for donor recruitment and blood screening and processing have decreased the risks associated with receiving a blood transfusion. If your child is assigned to the higher hematocrit level he/she may receive more blood transfusions and if assigned to the lower hematocrit level may receive fewer transfusions. Both the higher hematocrit and lower hematocrit levels are within the range of hematocrit levels normally used in the NICU to determine when to give a red blood cell transfusion.

There is a risk of loss of confidentiality when completing the cost of care survey. Your survey will be identified by a study ID number and only be used by the study investigators.

Benefits

There may be no benefit to your child from participating in this study. There may be benefit to your child if it turns out that either the higher hematocrit or lower hematocrit level show benefit. It is hoped that information gained from this study will help premature infants in the future.

There is no benefit to you or your child for completing the cost of care survey.

Alternatives to Study Participation

The only alternative is to not participate in this research study. Your choice will not affect the usual medical care your child will receive.

Financial Information

There will be no cost to you or your insurance company for your child's participation in this study. You will not be paid for your child's participation in this study.

All procedures and medications that are given as standard of care will be the responsibility of you and your insurance. This will include complete blood counts (CBC) and blood transfusions ordered by your child's doctor.

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Principal Investigator: Michele Walsh, MD

Research Related Injury

If injury occurs as a result of your child's involvement in this research, medical treatment is available from University Hospitals or another medical facility but your/your medical insurance will be responsible for the cost of this treatment. A research related injury is an injury that happens as a result of taking part in a research study. If you are injured by a medical treatment or procedure that you would have received even if you were not in the study, that is not considered a 'research injury.' There are no plans for payment of medical expenses or other payments. Including lost wages, for any research related injury. To help avoid injury, it is very important to follow all study directions.

Confidentiality

Information collected for this study will be sent electronically to a central data center via a dedicated, password sensitive computer. Your child will be identified by a study number and not by name or other identifying information.

If it is necessary for the study personnel to contact you or your child at a later time for follow-up, we will contact you at the address and/or telephone numbers you have provided. If we cannot locate you at the address or telephone numbers you have provided, we may use other information in the medical record such as social security numbers, your child's pediatrician or other contact information. We may contact you or your child until he/she reaches school age (6-7 years).

Privacy of Protected Health Information

The Health Insurance Portability & Accountability Act (HIPAA) is a Federal law that helps to protect the privacy of your child's health information and to whom this information may be shared within and outside of University Hospitals. This Authorization form is specifically for a research study entitled "TRANSFUSION OF PREMATURES (TOP)–DOES A LIBERAL RED BLOOD CELL TRANSFUSION STRATEGY IMPROVE NEUROLOGICALLY-INTACT SURVIVAL OF EXTREMELY-LOW-BIRTH-WEIGHT INFANTS AS COMPARED TO A RESTRICTIVE STRATEGY" and will tell you what health information (called Protected Health Information or PHI) will be collected for this research study, who will see your child's PHI and in what ways they can use the information. In order for the Principal Investigator, Dr. Michele Walsh and the research study staff to collect and use your child's PHI, you must sign this authorization form. You will receive a copy of this signed Authorization for your records. If you do not sign this form, your child may not join this study. Your decision to allow the use and disclosure of your child's PHI is voluntary and will have no impact on your child's treatment at University Hospitals. By signing this form, you are allowing the researchers for this study to use and disclose your child's PHI in the manner described below.

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Principal Investigator: Michele Walsh, MD

Generally the Principal Investigator and study staff at University Hospitals and Case Western Reserve University who are working on this research project will know that your child is in a research study and will see and use your child's PHI. The researchers working on this study will collect the following PHI about your child: information about your child while in the NICU including results of blood counts, information about blood transfusions, feedings and medications and his/her growth and development at 2 years of age. This PHI will be used to find out if higher or lower hematocrit levels for transfusion will result in improved outcomes at 2 years of age. Your access to your child's PHI may be limited during the study to protect the study results.

Your child's PHI may also be shared with the following groups/persons associated with this research study or involved in the review of research: National Institute of Child Health and Human Development, National Heart, Lung and Blood Institute, Research Triangle Institute, participating centers of the Neonatal Research Network, other staff from the Principal Investigator's medical practice group; University Hospitals, including the Center for Clinical Research and the Law Department; Government representatives or Federal agencies, when required by law.

Your permission to use and disclose your child's PHI does not expire. However, you have the right to change your mind at any time and revoke your authorization. If you revoke your authorization, the researchers will continue to use the information that they previously collected, but they will not collect any additional information. Also, if you revoke your authorization your child may no longer be able to participate in the research study. To revoke your permission, you must do so in writing by sending a letter to Dr. Michele Walsh, 11100 Euclid Avenue, Cleveland, OH 44106-6010. If you have a complaint or concerns about the privacy of your health information, you may also write to the UH Privacy Officer, Management Service Center, 3605 Warrensville Center, MSC 9105, Shaker Heights, OH 44122 or to the Federal Department of Health and Human Services (DHHS) at DHHS Regional Manager, Office of Civil Rights, US Department of Health and Human Services Government Center, JF Kennedy Federal Building, Room 1875, Boston, MA 02203. Complaints should be sent within 180 days of finding out about the problem.

The researchers and staff agree to protect your child's health information by using and disclosing it only as permitted by you in this Authorization and as directed by state and Federal law. University Hospitals is committed to protecting your child's confidentiality. Please understand that once your child's PHI has been disclosed to anyone outside of University Hospitals, there is a risk that your child's PHI may no longer be protected; however other Federal and State laws may provide continued protection of your child's information.

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Principal Investigator: Michele Walsh, MD

Summary of your rights as a participant in a research study

Your child's participation in this research study is voluntary. Refusing to participate will not alter your child's usual health care or involve any penalty or loss of benefits to which your child is otherwise entitled. If you decide for your child to join the study, you may withdraw at any time and for any reason without penalty or loss of benefits. If information generated from this study is published or presented, your child's identity will not be revealed. In the event new information becomes available that may affect the risks or benefits associated with this study or your willingness for your child to participate in it, you will be notified so that you can decide whether or not to continue participating. If your child experiences physical injury or illness as a result of participating in this research study, medical care is available at University Hospitals Case Medical Center (UHCMC) or elsewhere; however, UHCMC has no plans to provide free care or compensation for lost wages.

Disclosure of your study records

Efforts will be made to keep the personal information in your child's research record private and confidential, but absolute confidentiality cannot be guaranteed. The University Hospitals Case Medical Center Institutional Review Board may review your child's study records. If this study is regulated by the Food and Drug Administration (FDA), there is a possibility that the FDA might inspect your child's records. In addition, for treatment studies, the study sponsor and possibly foreign regulatory agencies may also review your child's records. If your child's records are reviewed your child's identity could become known.

Contact information

_____ has described to you what is going to be done, the risks, hazards, and benefits involved. The Principal Investigator Dr. Michele Walsh can also be contacted at 216-844-3759. If you have any questions, concerns or complaints about the study in the future, you may also contact them later.

If the researchers cannot be reached, or if you would like to talk to someone other than the researcher(s) about; concerns regarding the study; research participant's rights; research- related injury; or other human subject issues, please call the University Hospitals Case Medical Center's Research Subject Rights phone line at (216) 983-4979 or write to: The Chief Medical Officer, The Center for Clinical Research, University Hospitals Case Medical Center, 11100 Euclid Avenue, Lakeside 1400, Cleveland, Ohio, 44106-7061.

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Principal Investigator: Michele Walsh, MD

Signature

Signing below indicates that you have been informed about the research study in which you voluntarily agree for your child to participate; that you have asked any questions about the study that you may have; and that the information given to you has permitted you to make a fully informed and free decision about your child's participation in the study. By signing this consent form, you do not waive any legal rights, and the investigator(s) or sponsor(s) are not relieved of any liability they may have. A copy of this consent form will be provided to you.

X	
Name of Participant	
X	
Signature of Parent/Legal Guardian	Date
X	
Printed name of Parent/Legal Guardian	
X	
If Legal Guardian, indicate relationship to child	

X	
Signature of Witness	Date
X	
Printed Name of Witness	

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Principal Investigator: Michele Walsh, MD

X	
Signature of person obtaining informed consent	Date
X	
Printed name of person obtaining informed consent	
X	
Signature of Principal Investigator	Date
X	
Printed name of Principal Investigator	

STUDY 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?

FUNDING ORGANIZATION:

Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) /National Institutes of Health (NIH)

PRINCIPAL INVESTIGATOR: Kurt R. Schibler, MD

Pager #: (513) 736-5649
Office Telephone #: (513) 636-3972

INTRODUCTION

We are asking for your permission for your baby to be in a research study so that we can learn new information that may help others. If you decide not to give your permission for your baby to be in this study, we will still take good care of him/ her. If you decide to allow your baby to be in this study, you may change your mind at any and your baby can stop being in the study. Take all the time you need to make your choice. Ask us any questions you have; it is also okay to ask more questions after you decide to allow your baby to be in the study. You may ask questions at any time.

WHY ARE WE DOING THIS RESEARCH?

Doctors and nurses need to better understand when is the best time for premature infants to be given transfusions of blood. Blood contains red cells, which carry a molecule called hemoglobin.

Hemoglobin is essential for life as it carries oxygen around the body. Hemoglobin can be measured; it is used by doctors as a measure of how many red blood cells are circulating in your baby's body.

Because premature babies need intensive care, they need a lot of blood tests to monitor their care. Doctors try their best to order only a few blood tests depending on the needs of the premature babies. Since premature babies cannot make red blood cells easily, they sometimes become anemic and thus, they require blood transfusions.

When the hemoglobin falls below a certain level, doctors will transfuse the baby. However, we know that some doctors tend to use a higher level of hemoglobin and some doctors tend to use a lower level of hemoglobin. Our NICU doctors have tended to use a lower level of hemoglobin for transfusion because it has been shown to be safe in studies of extremely premature infants. The reason we are doing this study is that we do not really know which level of hemoglobin is better.

This study has been designed to gather information to understand at which level of hemoglobin we should transfuse for the best results.

We are asking that your baby take part in this research study because he /she has been born very early and is receiving care in the NICU.

WHO IS IN CHARGE OF THE RESEARCH?

Kurt Schibler, MD is the researcher at Cincinnati Children's Hospital Medical Center (CCHMC) that is in charge of this study.

CCHMC is being paid by the National Institutes of Health (NIH) to do this study.

This study has been approved and funded by the National Heart, Lung and Blood Institute and the Eunice Kennedy Shriver National Institute of Child Health and Human Development, branches of the National Institutes of Health and 18 large hospitals in the US are doing this study.

Information about this study is available on a public registry website (http://clinicaltrials.gov/ Identifier: NCT 01702805).

WHO SHOULD NOT BE IN THE STUDY?

Your baby cannot be in this study for any of the following reasons:

- You (parent or guardian) are opposed to the transfusion of blood
- Your baby has had a blood transfusion between 6 hours of life and time of randomization
- It is unlikely that you (your family) will be available for follow-up at 22 - 26 months

WHAT WILL HAPPEN IN THE STUDY?

Babies like yours, who are born very premature and who need intensive care, require a lot of blood tests. Because they cannot form new blood cells as fast as they are being removed, very premature babies become anemic and often require blood transfusion. We know that 90% of babies like yours receive at least one blood transfusion during their stay in the intensive care unit.

Anemia is measured by the level of hemoglobin in the blood, and blood transfusions are given when hemoglobin falls below a certain level. It is routine to receive blood transfusions at hemoglobin levels based on your doctor's choice. We have found that some doctors tend to use the higher levels and some doctors tend to use the lower levels. This is because at this time, no one knows which level of hemoglobin is better.

The levels at which babies are being transfused in this study are well within the range at which doctors across the country routinely transfuse, we are just looking to establish the best level of hemoglobin for transfusing premature babies.

Hospital - Inpatient Stage:

Once eligibility has been determined and if you agree to allow your baby to participate in the research study, the following will occur:

1. Your baby will be randomly assigned (like a flip of a coin) to either the higher level of hemoglobin or the lower level of hemoglobin. Both of these levels are within the usual range used by doctors in the NICU around the country. The doctor will use this level of hemoglobin to decide when to transfuse the baby, if a transfusion is needed as part of your baby's clinical care.

2. If your baby were to get unexpectedly ill or have an unexpected urgent need for blood transfusion (a point at which all doctors would routinely give blood), your baby would get the transfusion regardless of the level of hemoglobin.

3. All blood tests are done, at the request of your baby's doctor, as part of the routine standard of care. There are no extra blood tests being done on your baby.

4. A member of the study team will review certain parts of your baby's medical record and collect information about your baby's feeding, growth, medications, and medical conditions.

5. In order to complete the study visit at 22 - 26 months, it is important that we maintain contact with you. Before going home from the hospital, the study staff will ask you to provide contact phone numbers that will help us follow your baby after he/ she is discharged. We will ask you to provide information that will help us communicate with you in case you move or change your phone number (e.g., names of contacts, name of your baby's pediatrician, and permission to use public internet social and search pages).

Follow-Up Stage:

After discharge form the NICU, all extremely premature babies are routinely seen in the Follow-Up Clinic, in order to check how well they develop and grow.

In order to ensure that your baby has been scheduled for the 22 to 26 - month follow-up visit, we will again ask for updates to your contact information, including home address, home and cell phone numbers, email address, and confirm your agreement for us to use public internet social and search pages.

1. As part of this clinical and/ or research visit, at your child's 22 to 26 - month visit to the High Risk Infant Follow-Up Clinic he/ she will have:
   - A basic health check, including a neurological examination

2. For the purpose of this research study, the developmental psychometrist will meet with your child, and she will administer the Bayley exam. This is a standard test that is commonly used in the assessment of child development, child behavior, and neurological assessment.

3. For the purpose of this research study, the psychometrist, through an interview with the caregiver, will complete the following questionnaires:
   - Medical History (information about your baby's health)
   - Socio-Economic Status (SES) at discharge, such as questions relating to the composition of the baby's household and the education level of the baby's primary caretaker
   - Socio-Economic Status (SES) at 22 - 26 months of age (similar to the questions above)
   - The Brief Infant-Toddler Social and Emotional Assessment (BITSEA), which evaluates your baby's social and emotional behavior.

During the testing the children are observed playing with toys and moving around the room.

You will also be asked questions about your child's health since discharge home. This testing is routine for premature babies and will be done at no additional cost to you.

By signing this consent you are giving us your permission to collect the results of these evaluations. You and your child's doctor will be given the results of these tests and they will be explained to you.

Currently, the 22 to 26 - month visit is the end point of the study; however, we may contact you beyond this time in the event that study analysis shows a need for continued follow-up.

WHAT ARE THE GOOD THINGS THAT CAN HAPPEN FROM THIS RESEARCH?

There may be no benefit to your baby from participating in this study. However, we may discover developmental problems that your baby might have during this follow-up stage of the study. This would provide an opportunity, if necessary, for early interventions.

It is hoped that information gained from this study will benefit other babies in the future who have been born very premature.

WHAT ARE THE BAD THINGS THAT CAN HAPPEN FROM THIS RESEARCH?

This study does not pose any risks to your baby beyond what is encountered in the usual medical care of preterm babies, which varies among hospital practices..

This study does not alter the routine care for your baby. The risks associated with this study are exactly the same risks that exist in current medical practice and in blood transfusion therapy. If your baby needs blood for emergency reasons, your doctor will order the blood your baby needs – irrespective of the study. After that urgent need is over, your doctors will then return to the study protocol.

Blood transfusions are, in general, reasonably safe. You will be told about the risks of blood transfusion separately and will need to give your permission before the first transfusion is given. Giving blood transfusions when the baby's hemoglobin level is too high may result not only in more blood transfusions, but the babies may take longer to mature their own bone marrow to produce their own blood. On the other hand, transfusing when the baby's hemoglobin level is too low could lead to the baby not having enough hemoglobin to carry enough oxygen around the body, which can strain the heart and lungs. During this study, we will try to avoid these extremes by transfusing within the ranges of hemoglobin level that doctors currently use as part of standard care, but which varies among hospital practices.

During the entire study, an independent committee will review this study to make sure that it continues to be safe.

WHAT OTHER CHOICES ARE THERE?

Instead of being in this research study you may choose not to participate. If you choose not to participate in the study, it will not affect your care or your baby's care at this hospital. Your baby will receive the same health care even if you do not participate in the study.

If you choose not to participate in this study and if your baby needs a blood transfusion, the doctor will decide which level of hemoglobin to use in making the decision to transfuse your baby according to his or her judgment.

HOW WILL INFORMATION ABOUT YOUR CHILD BE KEPT PRIVATE?

Making sure that information about your child remains private is important to us.

The research staff at Cincinnati Children's Hospital Medical Center will keep records of your baby's participation in this study. These study records will include the results of tests your infant will undergo during the study and/ or tests administered before the study. The study records will also include other medical information relating to your infant's participation in this study. All study records will be stored in locked cabinets in the research offices located at Cincinnati Children's Hospital Medical Center.

Your baby's study records will be assigned a code number that will also be used to report results of laboratory assessments.

The researchers, including those directly involved in the study, or other collaborating researchers, may publish reports or articles on the study. You or your baby will not be identified by name in any published reports or written articles.

Personnel from Cincinnati Children's Hospital Medical Center, in order to monitor the conduct of the study, may review your baby's study records for this purpose.

Health care providers, other than the providers at Cincinnati Children's Hospital Medical Center that treat your baby during participation in this study, or that treated your infant prior to entry into the study, may provide your infant's medical records to the study staff for review during this study; if necessary, the study doctor will provide information back to your infant's primary care physician.

A copy of this consent form will be included in your baby's medical and research records.

Your baby will be registered in the Cincinnati Children's Hospital Medical Center's computer system as a research participant.

By signing this consent form you are giving permission for representatives of the Cincinnati Children's Hospital Medical Center ("CCHMC"), including the investigator, Division of Neonatology employees involved with the research study, the Institutional Review Board, and the Office for Research Compliance and Regulatory Affairs, to be allowed to inspect sections of your baby's medical and research records that are related to this study.

Also, by signing this consent form you are giving permission to agents of the National Institutes of Health (NIH), the sponsor (NICHD) and/ or the sponsor's agents (the Research Triangle Institute), regulatory agencies, such as the Office for Human Research Protections (OHRP), Department of Health and Human Services (HHS) to be allowed to inspect sections of your baby's medical and research records that are related to this study.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify your child. At most, the website will include a summary of the study results. You can search this website at any time.

WHAT IF WE LEARN NEW INFORMATION DURING THE RESEARCH?

The study doctor will tell you if they find out about new information from this or other studies that may affect your child's health, safety, or your willingness for your child to stay in this study.

WILL IT COST YOU ANYTHING EXTRA FOR YOUR CHILD TO BE IN THE RESEARCH STUDY?

There are no additional costs associated with participation in this research study.

Funds are not available to cover the cost of your baby's medical care; you remain responsible for the cost of non-research related care.

WILL YOU/ YOUR CHILD BE PAID TO BE IN THIS RESEARCH STUDY?

You will receive no payment for your child's participation in this research study. We will assist you with transportation needs, if you have them, in order to complete the study.

We will also provide your child with a developmentally appropriate toy at the end of the study visit.

WHAT HAPPENS IF YOUR CHILD IS INJURED FROM BEING IN THIS STUDY?

If you believe that your infant has been injured as a result of participation in biomedical or behavioral research you are to contact Dr. Kurt Schibler (513-636-3972) or the Director of Social Services (513-636-4711) to discuss the concerns.

Cincinnati Children's Hospital Medical Center follows a policy of making all decisions concerning compensation and/ or medical treatment for physical injuries occurring during or caused by participation in biomedical or behavioral research on an individual basis.

WHOM DO YOU CALL IF YOU HAVE QUESTIONS OR PROBLEMS?

For questions, concerns, or complaints about this research study you can contact Dr. Schibler as listed on page 1 of this document.

If you would like to talk to someone that is not part of the research staff or if you have general questions about your research study rights or questions, concerns, or complaints about the research, you can call the CCHMC Institutional Review Board at 513-636-8039.

AUTHORIZATION FOR USE/ DISCLOSURE OF HEALTH INFORMATION FOR RESEARCH:

To be in this research study you must also give your permission (or authorization) to use and disclose (or share) your child's "protected health information" (called PHI for short).

What protected health information will be used and shared during this study?
CCHMC will need to use and share your child's PHI as part of this study. This PHI will come from:
- Your child's CCHMC medical records
- Your child's research records

The types of information that will be used and shared from these records include:
- Laboratory test results, diagnosis, and medications
- Reports and notes from clinical and research observations
- Imaging (like CT scans, MRI scans, x-rays, etc.) studies and reports
- If applicable, information concerning HIV testing or the treatment of AIDS or AIDS-related conditions, drug or alcohol abuse, drug-related conditions, alcoholism, and/or psychiatric/psychological conditions (but not psychotherapy notes).

Who will share, receive and/or use your child's protected health information in this study?
- Staff at all the research study sites (including CCHMC)
- Personnel who provide services to your child as part of this study
- Other individuals and organizations that need to use your child's PHI in connection with the research, including people at the sponsor and organizations that the sponsor may use to oversee or conduct the study.
- The members of the CCHMC Institutional Review Board and staff of the Office of Research Compliance and Regulatory Affairs.

How will you know that your child's PHI is not misused?
People that receive your child's PHI as part of the research are generally limited in how they can use your child's PHI. In addition, most people who receive your child's PHI are also required by federal privacy laws to protect your child's PHI. However, some people that may receive your child's PHI may not be required to protect it and may share the information with others without your permission, if permitted by the laws that apply to them.

Can you change your mind?
You may choose to withdraw your permission at any time. A withdrawal of your permission to use and share your child's PHI would also include a withdrawal from participation in the research study. If you wish to withdraw your permission to use and share your child's PHI you need to notify the study doctor, listed on the first page of this document, in writing. Your request will be effective immediately and no new PHI about your child will be used or shared. The only exceptions are (1) any use or sharing of PHI that has already occurred or was in process prior to you withdrawing your permission and (2) any use or sharing that is needed to maintain the integrity of the research.

Will this permission expire?
Your permission will expire at the end of the study. If the study involves the creation or maintenance of a research database repository, this authorization will not expire.

Will your child's other medical care be impacted?
By signing this document you agree for child to participate in this research study and give permission to CCHMC to use and share your child's PHI for the purpose of this research study. If you refuse to sign this document your child will not be able to participate in the study. However, your child's rights concerning treatment not related to this study, payment for services, and enrollment in a health plan, or eligibility of benefits will not be affected.

SIGNATURES

The research team has discussed this study with you and answered all of your questions. Like any research, the researchers cannot predict exactly what will happen. Once you have had enough time to consider whether your baby should participate in this research you will document your permission by signature below.

You will receive a copy of this signed document for your records.

_____ _____

Signature of Participant's Parent or Legally Authorized Representative* Date

_____

* If signed by a legally authorized representative, a description of such representative's authority must be provided

_____

Printed Name of Research Participant (Baby)

_____ _____

Signature of Individual Obtaining Consent Date

DUKE UNIVERSITY HEALTH SYSTEM

Consent To Participate In A Research Study

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

You are being asked to allow your baby to take part in this research study because your baby was born prematurely and may require a blood transfusion while in the NICU (Neonatal Intensive Care Unit). Most babies like yours, who are born extremely prematurely and who need intensive care, require blood transfusion to treat their anemia. They develop anemia for a lot of reasons including the many blood tests they have, the inability of their bone marrow to make blood cells at a fast enough rates and others. We know that 90% of babies like yours receive at least one blood transfusion during their stay in the intensive care unit.

Research studies include only people who choose to take part. Study participation is voluntary. Please read this consent form carefully and take your time making your decision. As your baby's study doctor or study staff discusses this consent form with you, please ask him/her to explain any words or information that you do not clearly understand. We encourage you to talk with your family and friends before you decide to allow your baby to take part in this research study. The nature of the study, risks, inconveniences, discomforts, and other important information about the study are listed below.

Please tell the study doctor or staff if your baby is taking part in another research study.

Dr. Michael Cotten and the Neonatal/Perinatal Research Unit at Duke University Medical Center (DUMC), National Heart, Lung and Blood Institute and National Institutes for Child Health and Human Development (NICHD) Neonatal Research Network are conducting this study. A grant from the National Institutes of Health (NIH) will sponsor this study**,** and these funds may pay part of Dr. Cotten's salary.

WHO WILL BE MY BABY'S DOCTOR ON THIS STUDY?

If you decide to allow your baby to participate, Dr. Cotten will be your baby's doctor for the study and will be in contact with your baby's regular health care provider throughout the time that your baby is in the study and afterwards, if needed.

WHY IS THE STUDY BEING DONE?

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 includes multiple interventions to take care of their physiologic needs. Many of these aspects of care, including the best blood levels to maintain, have not been established.

The purpose of this study is to determine the best way to use hemoglobin or hematocrit levels for deciding when to give blood transfusions to very premature 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. However, we know that some doctors tend to use a higher level of hemoglobin/hematocrit and some doctors tend to use a lower level of hemoglobin/hematocrit when making this decision. The reason for this is that we do not know which level of hemoglobin/hematocrit 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. .

A description of this clinical trial will be 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 MANY BABIES WILL TAKE PART IN THIS STUDY?

About 1824 babies will take part in this study from different hospitals across the country. At this hospital, approximately 300 babies will participate in the study.

WHAT IS INVOLVED IN THIS STUDY?

If you agree to have your baby participate in the study, and you sign and date this consent form, 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. The doctor will use this level of hemoglobin/hematocrit to decide when to transfuse the baby.

If your baby were to get ill unexpectedly or have an unexpected urgent need for blood transfusion (where every baby would routinely receive blood), your baby would get the transfusion regardless of the level of hemoglobin/hematocrit.

All of the blood tests that are done are routine standard of care. We will ask you to complete an economic questionnaire that will help provide us with information as to how families cope with having a baby in the intensive care nursery.

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.

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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. ***All babies in the study will have the following:*** We will record your baby's birth weight, gestational age, and vital signs. We will record weekly:

- your baby's weight, and most recent head circumference,
- your baby's hemoglobin/hematocrit test results information from your baby's medical chart, including each transfusion, lab results, head ultrasound and any diagnoses your baby may have while in the NICU.

All babies who participate in the study will return to the High Risk Infant Follow-up Clinic between the age of 22 and 26 months. At this follow-up visit, which will take approximately two hours, we will do a medical exam and developmental testing, and check weight, length, and head circumference.

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

During Hospital Stay	After Discharge
Birth to 36 weeks PMA (post-menstrual age, or when you would have been 36 weeks along in your pregnancy)	Follow-up visit at 22-26 months of age
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.
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.
This phase ends when baby is discharged from the hospital or when the baby is 36 weeks PMA)	We will have you complete a questionnaire about home and family

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HOW LONG WILL MY BABY BE IN THIS STUDY?

If you agree for your baby to take part in this study, your baby's involvement will last until your baby is 22-26 months old. You will be asked to provide information while your baby is in the NICU, and information will be gathered at a follow-up visit when he or she is 22-26 months old.

You can choose to stop your baby's participation at any time without penalty or loss of any benefits to which your baby is entitled. However, if you decide to stop participation in the study, we encourage you to talk to your baby's doctor first.

WHAT ARE THE RISKS OR SIDE EFFECTS TO BEING IN THIS STUDY?

Your baby has been born very early, and is at risk for complications of extreme prematurity. Some of these babies die and some survivors have significant neurologic problems when they are older. There are no extra blood tests being done on your baby. All blood tests are done as routine standard of care at your doctor's request. This study does not alter the routine care for your baby, although it does direct the level of hemoglobin/hematocrit at which a transfusion will be given. The risks associated with this study are exactly the same risks that exist in current medical practice and in blood transfusion therapy. If your baby needs blood for emergency reasons, where all doctors would routinely give blood, they will get the blood they need – irrespective of the study. After that urgent need is over, decisions will be made according to the study protocol.

Blood transfusions are nowadays, in general extremely safe. However, giving blood transfusions at too high a hemoglobin/hematocrit level may result not only in more blood transfusions, but the babies may take longer to mature their own bone marrow to produce their own blood. On the other hand, transfusing at too low a hemoglobin/hematocrit could result in the baby not having enough hemoglobin to carry enough oxygen around the body. We avoid these extremes by transfusing within the ranges of hemoglobin/hematocrit level that doctors nowadays already use.

There is a chance that rate of death 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.

WHAT ARE THE BENEFITS TO BEING IN THIS 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 DO I HAVE IF I DO NOT ALLOW MY BABY TO TAKE PART IN THIS STUDY?

If you choose not to allow your baby to participate in this study and if your baby needs a blood transfusion, the doctor will decide based on their experience when to transfuse your baby.

WILL MY BABY'S INFORMATION BE KEPT CONFIDENTIAL?

Clinical information will be collected from both you and your baby's chart by a member of the Duke Neonatal-Perinatal Research Unit's team. Study records that identify your baby will be kept confidential as required by law. Federal Privacy Regulations provide safeguards for privacy, security, and authorized access. Except when required by law, your baby will not be identified by name, social security number, address, telephone number, or any other direct personal identifier except for date of birth and other event dates in study records disclosed outside of Duke University Health System (DUHS). For records disclosed outside of DUHS, your baby will be assigned a unique code number. The key to the code will be kept in a locked file in the research team's office. As part of the study, Dr. Cotten and his study team will report your baby's study data to NIH through their data collection center, Research Triangle Institute (RTI).

To meet federal, state and institutional regulations or for reasons related to this research, the study investigator may share a copy of this consent form and records that identify your child with the following people:

- the sponsor (NICHD) and/or the sponsor's agents (the Research Triangle Institute);
- the Department of Health and Human Services;
- regulatory agencies such as the Food and Drug Administration (FDA),
- representatives of NIH,
- the Duke University Health System Institutional Review Board.

If any of these groups review your baby's research record, they may also need to review the entire medical record. This information may be further disclosed by the sponsor of this study, NICHD. If disclosed by the sponsor, the information is no longer covered by the federal privacy regulations. If this information is disclosed to outside reviewers for audit purposes, it may be further disclosed by them and may not be covered by the federal privacy regulations.

Research records will be kept confidential to the extent provided by law, and will be maintained in the study record, at minimum, until your baby reaches the age of 21 years or for 6 years after the research is complete, whichever is longer.

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When research results from this study are reported in a professional setting, such as in a medical journal or at a scientific meeting, the identity of any baby taking part in the study is withheld.

WHAT ARE THE COSTS OF TAKING PART IN THIS STUDY?

There will be no additional costs to your baby as a result of being in this study. However, routine medical care for your baby's condition (care your baby would have received whether or not your baby was in this study) will be charged to you and your baby's insurance company. You may wish to contact your baby's insurance company to discuss this further. The 22-26 month follow up visit is considered standard of care and will be charged to you and your baby's insurance.

WHAT ABOUT RESEARCH RELATED INJURIES?

Immediate necessary medical care is available at Duke University Medical Center in the event that your baby is injured as a result of his/her participation in this research study. However, there is no commitment by Duke University, Duke University Health System, Inc., or your baby's Duke Physicians to provide monetary compensation or free medical care to your baby in the event of a study-related injury.

For questions about the study or a research-related injury, or if you have complaints, concerns or suggestions about the research contact Dr. Cotten at 919-681-6025 during regular business hours and at 919-970-4381 (pager) after hours and on weekends and holidays. You may also call the clinical research pager 24 hours a day at 919-970-1425 and speak to a member of the Neonatology Clinical Research team.

IS THERE COMPENSATION FOR TAKING PART IN THIS STUDY?

If your baby is not already participating in a Neonatal Research Network follow up study where compensation is provided, you will receive $100 to help cover travel expenses (meals, parking, transportation, etc.) at 22-26 month clinic. There is no other compensation for participating in this study.

WHAT ABOUT MY RIGHTS TO DECLINE PARTICIPATION OR WITHDRAW MY BABY FROM THE STUDY?

You may choose not to allow your baby to be in the study, or, if you agree to the study, you may withdraw your baby from the study at any time. If you withdraw your baby from the study, no new data about your baby will be collected for study purposes unless the data concern an adverse event (a bad effect) related to the study. If such an adverse event occurs, we may need to review your baby's entire medical record. All data that have already been collected for study purposes, and any new information about an adverse event related to the study, will be sent to the study sponsor.

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Your decision not to participate or to withdraw your baby from the study will not involve any penalty or loss of benefits to which you or your baby are entitled, and will not affect your baby's access to health care at Duke. If you do decide to withdraw your baby, we ask that you contact Dr. Cotten in writing and let him know that you are withdrawing your baby from the study. His mailing address is: 2424 Erwin Road, Suite 504, DUMC Box 2739, Durham, North Carolina, 27705.

Dr. Cotton may decide to take your baby off this study if the study is ended early, or if he determines that it is no longer in your baby's best interest to continue. The sponsor or regulatory agencies may stop this study at any time without your consent.

We will tell you about new information that may affect your baby's health, welfare, or willingness to stay in this study.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

For questions about the study or a research-related injury, or if you have complaints, concerns or suggestions about the research, contact Dr. Cotten at 919-681-6024 during regular business hours and at pager 919-970-4381 (Cotten) after hours and on weekends and holidays. After business hours and on weekends and holidays, you may also page the clinical research team at 919-970-1425 and speak to a member of the Neonatology Clinical Research team.

For questions about your baby's rights as a research participant, or to discuss problems, concerns or suggestions related to the research, contact the Duke University Health System Institutional Review Board (IRB) Office at (919) 668-5111.

STATEMENT OF CONSENT

"The purpose of this study, procedures to be followed, risks and benefits have been explained to me. I have been allowed to ask questions, and my questions have been answered to my satisfaction. I have been told whom to contact if I have questions, to discuss problems, concerns, or suggestions related to the research, or to obtain information or offer input about the research. I have read this consent form and agree for my child to be in this study, with the understanding that I may withdraw my child at any time. I have been told that I will be given a signed and dated copy of this consent form."

_____ _____

Signature of Parent or Legal Guardian Date

_____ _____

Signature of Person Obtaining Consent Date

Emory University and Grady Health System
Consent to be a Research Subject

Title: **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?

Principal Investigator: Ravi Patel, MD

Sponsor: Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)
Neonatal Research Network
National Heart, Lung and Blood Institute

If you are the legal guardian of a child who is being asked to participate, the term "you" used in this consent refers to your child.

Introduction

You and your baby are being asked to be in a medical research study. This form is designed to tell you everything you need to think about before you decide to consent (agree) to be in the study or not to be in the study. **It is entirely your choice. If you decide to take part, you can change your mind later on and withdraw from the research study.** The decision to join or not join the research study will not cause you or your baby to lose any medical benefits. If you decide not to take part in this study, your doctor will continue to treat you and your baby.

Before making your decision:

- Please carefully read this form or have it read to you
- Please listen to the study doctor or study staff explain the study to you
- Please ask questions about anything that is not clear

You can take a copy of this consent form, to keep. Feel free to take your time thinking about whether you would like to participate. You may wish to discuss your decision with family or friends. Do not sign this consent form unless you have had a chance to ask questions and get answers that make sense to you. By signing this form you will not give up any legal rights.

A description of this clinical trial will be available on www.ClinicalTrials.gov, as required by U.S. law. This website will not include information that can identify you. At most the website will include a summary of the results. You may search this website at any time (http://clinicaltrials.gov/ Identifier: NCT 01702805).

Study Overview

This is a research study. We are inviting you and your baby to participate in this research study because you have delivered a baby who weighed 1000 g or less at birth. Your baby is also less than 29 weeks gestation. This study is trying to provide an answer to the question: "What is the best level of hemoglobin for transfusing blood to babies?"

Doctors and nurses need to better understand when we should transfuse blood (as red cells) into the blood of premature infants. Blood contains red cells. Red cells have a substance called hemoglobin. Hemoglobin is essential for life. Hemoglobin carries oxygen around the body. Hemoglobin can be measured. It is used by doctors as a measure of how many red blood cells are circulating in your baby's body.

Premature babies need intensive care. Your baby may need a lot of blood tests to monitor their care. Doctors try their best to order only a few blood tests depending on the needs of the premature babies. Premature infants cannot make red blood cells easily. They sometimes become anemic. Therefore, we have to give babies blood transfusions. We know that 90% of babies like yours receive at least one blood transfusion during their stay in the intensive care unit.

When the hemoglobin falls below a certain level, doctors will transfuse the baby with blood. Some doctors tend to use a higher level of hemoglobin. Some doctors tend to use a lower level of hemoglobin. The reason for this is that we do not know which level of hemoglobin is better.

This study has been approved and funded by the National Heart, Lung and Blood Institute and the Eunice Kennedy Shriver NICHD. We are planning to enroll 100 babies at Emory. A total of 1824 babies will participate nationwide at 18 medical centers.

Procedures

If you agree that your baby should take part in this study, your baby will be "randomized" into one of the two study groups described below. This randomization means that the group is chosen by a computer program. It is a random assignment. You have a 50/50 chance of ending up in either study group. One group is the higher level of hemoglobin for transfusions. The second group is the lower level of hemoglobin for transfusions. Both of these levels are in the usual range used by doctors in the intensive care nursery. The doctor will use this level of hemoglobin to decide when to transfuse your baby.

Sometimes babies get unexpectedly ill. They may have an unexpected, urgent need for blood transfusion. This is a time when your baby's doctor would routinely give blood. If your baby is in this study and this happens, your baby would get the transfusion regardless of the level of hemoglobin.

All of the blood tests that are done are part of the routine standard of care. The researchers will not order any additional blood test for your baby. As part of this research we will collect information about your child. We will collect lab results and information about any blood transfusions. We will collect information about your baby's vital signs and breathing support. We will also collect information about your baby's feedings and medications. We will follow your baby's growth. We will record any head ultrasound reports that are done as standard of care.

As part of our research, we will ask you to complete an economic questionnaire. This will help provide us with information as to how families cope with having a baby in the intensive care nursery. If you feel uncomfortable answering any question, you may leave the question blank.

Your baby will be followed for this study until he/she is discharged from the hospital. At 22-26 months after your baby's full-term due date, your child will be evaluated by developmental specialists. During the testing your child will be observed playing with toys and moving around the room. You will also be asked questions about your child's health since discharge home. This testing is done with the Emory Developmental Progress Clinic. This testing is routine for high-risk babies. It will be done at no cost to you. By signing this consent you are giving us your permission to collect the results of these evaluations. You and your child's doctor will be given the results of these tests and they will be explained to you. We may call you in the future for more long-term follow-up.

Risks and Discomforts

There may be side effects from the study procedures that are not known at this time.

The risks associated with this study are exactly the same risks that exist in current medical practice and in blood transfusion therapy. Your baby may need blood for emergency reasons. In this emergency, doctors would routinely give

blood. If this happens, your baby will get the blood they need – irrespective of the study. After that urgent need is over, they will then return to the study protocol.

Giving blood transfusions at too high a hemoglobin level may result in more blood transfusions. Also, babies may take longer to mature their own bone marrow to produce their own blood. Transfusing blood at too low a hemoglobin level could lead to the baby not having enough hemoglobin to carry enough oxygen around the body. We avoid these extremes by transfusing within the ranges of hemoglobin levels that doctors nowadays already use.

New Information

It is possible that the researchers will learn something new during the study about the risks of being in it. If this happens, they will tell you about it. Then you can decide if you want to continue to be in this study or not. You may be asked to sign a new consent form that includes the new information if you decide to stay in the study.

Benefits

This study is not designed to benefit you or your baby directly. However, your baby may benefit from additional monitoring during the study. The study results may be used to help others in the future.

Compensation

You will not be offered payment for being in this study. However, we will cover the cost of your time and travel to the Emory Developmental Progress Clinic for the visit at 22 to 26 months.

Other Treatment outside this Study

If you decide not to enter this study, there is care available to you outside of this research. If you choose not to participate in this study and if your baby needs a blood transfusion, the doctor will decide at which level of hemoglobin to use in making the decision to transfuse your baby. Your doctor can discuss this with you. Your baby does not have to be in this study to be treated for low hemoglobin while in the nursery.

Confidentiality

Certain offices and people other than the researchers may look at your medical charts and study records. Government agencies and Emory or Grady Health System employees overseeing proper study conduct may look at your study records. These offices include the Office for Human Research Protections, the Emory Institutional Review Board, the Grady Research Oversight Committee, the Emory Office of Research Compliance, the Office for Clinical Research, the Clinical Trials Audit & Compliance Office, the Research Triangle Institute, and the study sponsors including the Eunice Kennedy Shriver NICHD Neonatal Research Network and the National Heart, Lung and Blood Institute. Emory and Grady Health System will keep any research records we create private to the extent we are required to do so by law. A study number rather than your name will be used on study records wherever possible. Your name and other facts that might point to you will not appear when we present this study or publish its results.

Study records can be opened by court order. They may also be produced in response to a subpoena or a request for production of documents.

Research Information Will Go Into the Medical Record:

If you are or have been an Emory or Grady Health System patient, you have an Emory or Grady Health System medical record. If you are not and have never been an Emory or Grady Health System patient, you do not have one. Please note that an Emory or Grady Health System medical record **will** be created if you have any services or procedures done by an Emory or Grady Health System provider or facility for this study.

If you agree to be in this study, a copy of the consent form and HIPAA patient form that you sign **will** be placed in your Emory or Grady Health System medical record. Emory or Grady Health System may create study information about you

that can help Emory Healthcare take care of you. Anyone who has access to your medical record will be able to have access to all the study information placed there. The confidentiality of the study information in your medical record will be protected by laws like the HIPAA Privacy Rule. On the other hand, some state and federal laws and rules may not protect the research information from disclosure.

In Case of Injury

If you get ill or injured from being in the study, Emory or Grady Health System would help you to get medical treatment. Emory, Grady Health System, and the sponsor have not, however, set aside any money to pay you or to pay for this medical treatment. The only exception is if it is proved that your injury or illness is directly caused by the negligence of an Emory, Grady Health System, or sponsor employee. "Negligence" is the failure to follow a standard duty of care.

If you become ill or injured from being in this study, your insurer will be billed for your treatment costs. If you do not have insurance, or if your insurer does not pay, then you will have to pay these costs.

If you believe you have become ill or injured from this research, you should contact Dr. Ravi Patel at telephone number 404-727-5905. You should also let any health care provider who treats you know that you are in a research study.

Costs

There will be no costs to you for participating in this study. You will not be charged for any of the research activities. While you and your baby are in this study, the cost of all your medical care (procedures, medications, doctor visits, etc.) will continue to be billed to you or your insurance.

Withdrawal from the Study

You have the right to leave a study at any time without penalty. If you leave the study before your baby is discharged to home, the researchers may ask you to have some of the final steps done.

The researchers and sponsor also have the right to stop your participation in this study without your consent if:

- They believe it is in your infant's best interest;
- You were to object to any future changes that may be made in the study plan;
- Or for any other reason.

Contact Information

Contact Ellen Hale, RN, BS, CCRC at 404-778-1679 or ehale@emory.edu:

- if you have any questions about this study or your part in it,
- if you feel you have had a research-related injury or a bad reaction to the study drug, or
- if you have questions, concerns or complaints about the research

Contact the Emory Institutional Review Board at 404-712-0720 or 877-503-9797 or irb@emory.edu:

- if you have questions about your rights as a research participant.
- if you have questions, concerns or complaints about the research.
- You may also let the IRB know about your experience as a research participant through our Research Participant Survey at http://www.surveymonkey.com/s/6ZDMW75.

If you are a Grady Health System participant, you may also contact Dr. Curtis Lewis, Senior Vice President for Grady Health System Medical Affairs at (404) 616-4261.

Consent

Please, print your name and sign below if you agree to be in this study. By signing this consent form, you will not give up any of your legal rights. We will give you a copy of the signed consent, to keep.

_____
Name of Subject

_____ _____
Signature of Person Conducting Informed Consent Discussion Date Time

_____
Name of Person Conducting Informed Consent Discussion

_____ _____
Signature of Legally Authorized Representative Date Time

_____
Authority of Legally Authorized Representative or Relationship to Subject

Ravi Patel, MD
Division of Neonatology
2015 Uppergate Drive
Atlanta, GA 30322

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?

Dear Dr. Patel:

I want to end my participation in the research study that is named above. In addition to ending my participation I would like to [choose one of the following options]:

REVOKE MY AUTHORIZATION FOR THE RESEARCHERS TO COLLECT AND USE MY INFORMATION:

_____ I will not participate in the research study, and I revoke my authorization to permit the researchers to collect and use any more information about me. I understand and agree that in certain circumstances the researchers may need to use my information even though I have revoked my authorization, for example, to let me know about any safety concerns, or to make any required reports to governmental regulatory agencies.

CONTINUE MY AUTHORIZATION FOR THE RESEARCHERS TO COLLECT AND USE MY INFORMATION:

_____ I will not actively participate in the research study any more, but the researchers may continue to collect and use information from my medical record as needed for the research study, but only for the reasons discussed in the consent form that I signed.

I understand that the researchers will respond to this letter by letting me know that they have received it.

Sincerely,

_____ _____
Signature of Study Participant ----Date

Emory University Research Subject HIPAA Authorization to Use or Disclose Health Information that Identifies You for a Research Study

Title: 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?

Principal Investigator: Ravi Patel, MD

Sponsor: Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Neonatal Research Network
National Heart, Lung and Blood Institute

Introduction
The privacy of your health information is important to us. We call your health information that identifies you, your "protected health information" or "PHI." To protect your PHI, we will follow federal and state privacy laws, including the Health Insurance Portability and Accountability Act (HIPAA). We refer to all of these laws in this form as the Privacy Rules. This form explains how we will use your PHI for this study.

Please read this form carefully and if you agree with it, sign it at the end.

Description of Research Study This study involves babies who weigh 1000 grams or less at birth and who are less than 29 weeks gestation. This study is trying to provide an answer to the question: "What is the best level of hemoglobin for transfusing blood to babies?"

PHI That Will Be Used/Disclosed
Entire Medical Record

Purposes for Which Your PHI Will Be Used
If you sign this form, you give us your permission to use your PHI for the conduct and oversight of this research study.

People That Will Use or Disclose Your PHI and Purpose of Use/Disclosure
Different people and groups will use and disclose your PHI. They will do this only in connection with the research study. The following persons or groups may use and/or disclose your PHI:

- The Principal Investigator and the research staff.
- The Principal Investigator may use other people and groups to help conduct the study. These people and groups will use your PHI to do this work.
- Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Neonatal Research Network and the National Heart, Lung and Blood Institute are the Sponsors of this Research. The Sponsors may use and disclose your PHI to make sure the research is done correctly. They may also use your PHI to collect and analyze the results of the research. The Sponsor may have other people and groups help conduct, oversee, and analyze the study. These people or groups will use your PHI.
- The following groups may also use and disclose your PHI. They will do this to make sure the research is done correctly and safely. The groups are:
    - the Emory University Institutional Review Board

- the Emory University Office for Clinical Research
- the Emory Clinical Trials Audit & Compliance Office
- the Emory University Office of Research Compliance
- NRN Data Safety and Monitoring Committee (DSMC)
- any government agencies who regulate the research including the Office for Human Research Protections
- Grady Research Oversight Committee
- Research Triangle Institute
- Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Neonatal Research Network
- the National Heart, Lung and Blood Institute

We will use or disclose your PHI when we are required to do so by law. This includes laws that require us to report child abuse or elder abuse. We also will comply with legal requests or orders that require us to disclose your PHI. These include subpoenas or court orders.

Expiration of Your Authorization

As this is a research study, your authorization will not expire. You may, however, revoke your authorization later.

Revoking Your Authorization

You do not have to sign this form. Even if you do, at any time later on you may revoke (take back) your permission. If you want to do this, you must write to:

Ravi Patel, MD
Division of Neonatology
2015 Uppergate Drive
Atlanta, GA 30322

After that point, the researchers would not collect any more of your PHI. But they may use or pass along the information you already gave them so they can follow the law, protect your safety, or make sure the research was done properly. If you have any questions about this, please ask.

Other Items You Should Know

If we disclose information to people who do not have to follow the Privacy Rules, your information will no longer be protected by the Privacy Rules. People who do not have to follow the Privacy Rules can use or disclose your information with others without your permission if they are allowed to do so by the laws that cover them. Let us know if you have questions about this.

You do not have to sign this form. If you do not sign, you may not participate in the research study. You may still receive non-research related treatment.

We will put a copy of your signed informed consent form for the research study and your signed HIPAA Authorization form into any medical record that you may have with Emory Healthcare facilities.

During the study you will generally not have access to records related to the research study. This is to preserve the integrity of the research. You may have access to these records when the study is complete. These records may include research related PHI your health care providers use to make decisions about your care. If necessary for your care, this information may be available to your doctor before the end of the study.

If identifiers are removed from your PHI, then the remaining information will not be subject to the Privacy Rules. It may be used or disclosed with other people or organizations, and/or for other purposes.

Contacts

If you have any questions regarding the study, you may call Dr. Ravi Patel at 404-727-5905.
If you have any questions about the study, or your rights as a study subject, you may contact the Emory University Institutional Review Board at 404-712-0720 or 1-877-503-9797, by email at irb@emory.edu.

Authorization

A copy of this form will be given to you.

_____
Signature of Study Subject's Legal Authorized Representative

_____ _____
Date Time

_____
Printed Name of Study Subject's Legally Authorized Representative
Relationship to Study Subject: _____

_____
Signature of Person Obtaining Authorization

_____ _____
Date Time

_____
Printed Name of Person Obtaining Authorization

_____ _____
Date Time

INDIANA UNIVERSITY INFORMED CONSENT STATEMENT FOR

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

You and your baby are invited to participate in a study of blood transfusions (giving blood) in premature babies to better learn at which level of hemoglobin (this molecule carries oxygen) we should give blood to our babies so they might have better outcomes. Your baby qualifies because he/she was born early and has a high chance that they will receive at least one blood transfusion. We ask that you read this form and ask any questions you may have before agreeing to be in the study.

The study is being conducted by Dr. Brenda Poindexter from the Department of Pediatrics at Indiana University. It is funded by the National Institutes of Health (NIH), and sponsored by the National Institute of Child Health and Human Development (NICHD).

STUDY PURPOSE

The purpose of this study is to help doctors and nurses to better understand when we should give blood to our premature babies. Blood contains red cells, which carry a molecule called hemoglobin. Hemoglobin is necessary for life as it carries oxygen around the body. Hemoglobin is used by doctors as a measure of how many red blood cells are in your baby's body. Because premature babies need intensive care and cannot make red blood cells easily, they sometimes become anemic (where your body does not have enough healthy red blood cells and then can't provide enough oxygen to the body). Therefore, we have to give them blood. These blood transfusions are given when the hemoglobin falls below a certain level. It is routine to receive blood transfusions at hemoglobin levels based on your doctor's choice. We have found that some doctors tend to use the higher levels and some doctors tend to use the lower levels. This is because, at the moment, no one knows which level of hemoglobin is better. This study hopes to help us find out when we should best give blood to our babies.

NUMBER OF PEOPLE TAKING PART IN THE STUDY:

If you agree to participate, your baby will be one of 1824 babies from across the country who will also be participating in this research. Here, we will enroll about 100 babies.

PROCEDURES FOR THE STUDY:

The levels at which babies are being transfused in this study are well within the range at which doctors across the country routinely transfuse now, we are trying to establish what is the best level. This study is trying to give an answer to the question: "What is the best level of hemoglobin for transfusing babies?" If you agree that your baby can take part in this study, your baby will be randomly assigned (like a flip of a coin) to either the higher level of hemoglobin or the lower level. Both of these levels are in the usual range used by doctors in the NICU. The doctor will use this level of hemoglobin to decide when to transfuse the baby. If your baby was to get sick and immediately need a blood transfusion (when everyone would routinely give blood), your baby would get the blood no matter what the level of hemoglobin is/was.

All of the blood tests that are done are routine standard of care, ordered by your doctor, meaning this study does not ask for them. We will also ask you to complete a questionnaire that will help give us information as to how families cope with having a baby in the intensive care nursery.

Babies born this early are routinely seen in the Follow-up clinic when they are around 22 -26 months to check how well they are developing and growing. At this visit, they are observed playing with toys, how they walk, talk, and move around the room. We will also ask you to complete a short questionnaire about how your life and work schedule has been due to your baby's stay in the hospital.

RISKS OF TAKING PART IN THE STUDY:

While on the study, the risks are:

This study does not carry any extra risks to your baby if you choose to take part. There are no extra blood tests being done on your baby. This study does not change the care for your baby. The risks associated with this study are exactly the same risks that exist for your baby than any other baby who gets blood. Your baby's doctor will talk to you about this before giving blood. If your baby needs blood for emergency reasons, where all doctors would routinely give blood, they will get the blood they need – no matter what group they were in for the study. After that urgent need is over, they will then return to the study protocol.

Blood transfusions are nowadays extremely safe. To simplify, giving blood transfusions at a hemoglobin level that is too high may result, not only, in more blood transfusions, but these babies may take longer to mature their own bone marrow that helps to produce their own blood. On the other hand, transfusing at a hemoglobin level that is too low, could lead to these babies not having enough hemoglobin to carry enough oxygen around the body. We avoid these extremes by transfusing within the ranges of hemoglobin levels that doctors already use.

During the entire study, an independent committee will review this study to make sure that it continues to be safe.

The risks of completing the survey are being uncomfortable answering the questions and a possible loss of confidentiality.

BENEFITS OF TAKING PART IN THE STUDY:

This study may not directly benefit your baby. However, your baby may benefit from additional monitoring during the study.

ALTERNATIVES TO TAKING PART IN THE STUDY:

Instead of being in the study, you could choose not to participate. The standard of care for your infant will not change.

CONFIDENTIALITY

We will do our best to make sure that the personal information obtained during the course of this 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.

However, it is possible that other people may inspect and copy records pertaining to this research and this includes groups such as the federal government regulatory agencies, including the Office for Human Research Protections (OHRP), the U.S. Food and Drug Administration (FDA), The National Institute of Child Health and Human Development (NICHD), and its research designee (Research Triangle Institute-the data group) the NIH, and the study investigator, research associates and the Indiana University Institutional Review Board or its designees.

To help protect your and your baby's confidentiality, we will label information with a code number. The study logs linking the code number with your baby's identity will be kept in a locked office, in a locked file cabinet and on password-protected computer files. A copy of this Informed Consent Document will be placed in your and your baby's medical record and you will also get a copy.

A description of this clinical trial will be available on **ClinicalTrials.gov**, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

COSTS

You will not have any additional costs for being in this research study.

You and/or your medical/hospital insurance carrier will remain responsible for you and your baby's regular medical care expenses.

PAYMENT

At the follow-up visit at 22-26 months, you will be reimbursed for your travel expenses in the form of a gift card worth $75.00 to offset parking, gas, lunch and time off work.

COMPENSATION FOR INJURY

In the event of physical injury resulting from your participation in this research, necessary medical treatment will be provided to you and billed as part of your medical expenses. Costs not covered by your health care insurer will be your responsibility. Also, it is your responsibility to determine the extent of your health care coverage. There is no program in place for other monetary compensation for such injuries. However, you are not giving up any legal rights or benefits to which you are otherwise entitled.

CONTACTS FOR QUESTIONS OR PROBLEMS

For questions about the study or a research-related injury, contact Dr. Brenda Poindexter at 317-274-4768. If you cannot reach the researcher during regular business hours, and have questions about your rights being in research or to discuss problems or concerns, please call the IU Human Subjects Office at (317) 278-3458. After business hours, or in an emergency, please call the neonatologist on call at 317-948-4371.

For questions about your rights as a research participant or to discuss problems, complaints or concerns about a research study, or to obtain information, or offer input, contact the IU Human Subjects Office at (317) 278-3458.

VOLUNTARY NATURE OF STUDY

Taking part in this study is voluntary. You may choose for your baby not to take part or leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you or your baby are entitled. Your decision whether or not to participate in this study will not affect your current or future relations with Riley Hospital for Children at IU Health, Special Care Nursery at IU Health or Riley Hospital for Children at IU Health Methodist Hospital. We will tell you about new information that may affect your baby's health, welfare, or your willingness to allow your baby to stay in this study.

SUBJECT'S CONSENT

In consideration of all of the above, I give my consent for my baby to participate in this research study.

I will be given a copy of this informed consent document to keep for my records.

Baby's Printed Name:_____

Printed Name of Parent:_____

Signature of Parent:_____ Date:_____

Printed Name of Parent:_____

Signature of Parent:_____ Date:_____

Printed Name of Person Obtaining Consent:_____

Signature of Person Obtaining Consent:_____ **Date:**_____

For IRB Office Use ONLY

IRB Approval Date: Oct. 24, 2012
Expiration Date: Oct. 23, 2013

INDIANA UNIVERSITY
AUTHORIZATION FOR THE RELEASE OF HEALTH INFORMATION FOR RESEARCH

Introduction: You have the right to decide who may review or use your Protected Health Information ("PHI"). The type of information that may be used is described below. When you consider taking part in a research study, you must give permission for your PHI to be released from your doctors, clinics, and hospitals to the research team, for the specific purpose of this research study.

What does this authorization relate to? This authorization relates to the following study:

Brenda Poindexter, MD, MS

PRINCIPAL INVESTIGATOR (in charge of Research Team)	*IRB PROTOCOL # 1210009783*
	SPONSOR #
NAME OF RESEARCH PARTICIPANT	*BIRTHDATE*
STREET ADDRESS	*CITY, STATE & ZIP CODE*

What information will be used for research purposes? The PHI that will be used for research purposes may include some or all of your health records. This includes, but is not limited to: information provided by you directly to the Research Team, hospital records and reports; admission histories, and physicals; X-ray films and reports; operative reports; laboratory reports; treatment and test results; immunizations; allergy reports; prescriptions; consultations; clinic notes; and any other medical or dental records needed by the Research Team.

Specific Authorizations: I understand that this release also pertains to records concerning hospitalization or treatment that may include the categories listed below. I have the right to specifically request that records NOT be released from my health care providers to the Research Team. However, I understand that if I limit access to any of the records listed below, I may not be able to be in this research study. Check limitations, if any, below:

- ☐ Mental health records
- ☐ Psychotherapy Notes
- ☐ HIV (AIDS)
- ☐ Sexually transmitted diseases
- ☐ Alcohol / Substance abuse
- ☐ Other: _____

Who will be allowed to release this information?

I authorize the following persons, groups or organizations to disclose the information described in this Release of Information/Authorization for the above referenced research study:

- ☒ **Treating providers**
- ☒ **Hospitals, clinics or other places where I have received treatment**
- ☐ **Other:**_____
- ☒ **The Principal Investigator and the Research Staff**

Who can access your PHI for the study? The people and entities listed above may share my PHI (or the PHI of the individual(s) whom I have the authority to represent), with the following persons or groups for the research study: the Research Team, IU Institutional Review Board and its designees, Research Sponsor and its representatives, Research Organizations, the Department of Health & Human Services or other US or foreign government agencies as required by law, and to the Food and Drug Administration (FDA) or a person subject to the jurisdiction of the FDA in order to audit or monitor the quality, safety or effectiveness of the product or activity.

The **Research Team** includes the Principal Investigator, his/her staff, research coordinators, research technicians and other staff members who provide assistance to the Research Team. If there is a **Research Sponsor(s),** this shall include: The National Institutes of Health and any **Research Organizations** who provided assistance to the **Research Sponsor(s)** including, but not limited to: RTI International (RTI), their data center.

INDIANA UNIVERSITY
AUTHORIZATION FOR THE RELEASE OF HEALTH INFORMATION FOR RESEARCH

Expiration date of this Authorization: This authorization is valid until the following date or event:

☐ Specify Date ___/___/____ ☐ End of the Study
☐ Other: _____ ☒ None; authorization is valid indefinitely

Efforts will be made to ensure that your PHI will not be shared with other people outside of the research study. However, your PHI may be disclosed to others as required by law and/or to individuals or organizations that oversee the conduct of research studies, and these individuals or organizations may not be held to the same legal privacy standards as are doctors and hospitals. Thus, the Research Team cannot guarantee absolute confidentiality and privacy.

I have the right:

1. To refuse to sign this form. Not signing the form will not affect my regular health care including treatment, payment, or enrollment in a health plan or eligibility for health care benefits. However, not signing the form will prevent me from participating in the research study above.

2. To review and obtain a copy of my personal health information collected during the study. However, it may be important to the success and integrity of the study that persons who participate in the study not be given access until the study is complete. The Principal Investigator has discretion to refuse to grant access to this information if it will affect the integrity of the study data during the course of the study. Therefore, my request for information may be delayed until the study is complete.

3. To cancel this release of information/authorization at any time. If I choose to cancel this release of information/authorization, I must notify the Principal Investigator for this study **in writing** at: Brenda Poindexter, MD, MS at 699 Riley Hospital Drive, RR208, Indianapolis, IN 46202. However, even if I cancel this release of information/authorization, the Research Team, Research Sponsor(s) and/or the Research Organizations may still use information about me that was collected as part of the research project between the date I signed the current form and the date I cancel the authorization. This is to protect the quality of the research results. I understand that canceling this authorization may end my participation in this study.

4. To receive a copy of this form.

I have had the opportunity to review and ask questions regarding this release of information/authorization form. By signing this release of information/authorization, I am confirming that it reflects my wishes.

_____
Printed name of Individual/Legal Representative

_____
Signature of Individual/Legal Representative *Date*

**If signed by a legal representative; state the relationship and identify below the authority to act on behalf of the individual's behalf.*

***Individual is:** ☒ a Minor ☐ Incompetent ☐ Disabled ☐ Deceased

***Legal Authority:**

☐ Custodial Parent ☐ Legal Guardian ☐ Executor of Estate of the Deceased
☐ Power of Attorney Healthcare ☐ Authorized Legal Representative
☐ Other: _____

For IU Human Subjects Office Use ONLY

IRB REVIEWED
Oct. 24, 2012

INDIANA UNIVERSITY
AUTHORIZATION FOR THE RELEASE OF HEALTH INFORMATION FOR RESEARCH

Introduction: You have the right to decide who may review or use your Protected Health Information ("PHI"). The type of information that may be used is described below. When you consider taking part in a research study, you must give permission for your PHI to be released from your doctors, clinics, and hospitals to the research team, for the specific purpose of this research study.

What does this authorization relate to? This authorization relates to the following study:

Brenda Poindexter, MD, MS

PRINCIPAL INVESTIGATOR (in charge of Research Team)	*IRB PROTOCOL # 1210009783*
	SPONSOR #
NAME OF RESEARCH PARTICIPANT	*BIRTHDATE*
STREET ADDRESS	*CITY, STATE & ZIP CODE*

What information will be used for research purposes? The PHI that will be used for research purposes may include some or all of your health records. This includes, but is not limited to: information provided by you directly to the Research Team, hospital records and reports; admission histories, and physicals; X-ray films and reports; operative reports; laboratory reports; treatment and test results; immunizations; allergy reports; prescriptions; consultations; clinic notes; and any other medical or dental records needed by the Research Team.

Specific Authorizations: I understand that this release also pertains to records concerning hospitalization or treatment that may include the categories listed below. I have the right to specifically request that records NOT be released from my health care providers to the Research Team. However, I understand that if I limit access to any of the records listed below, I may not be able to be in this research study. Check limitations, if any, below:

- ☐ Mental health records
- ☐ Psychotherapy Notes
- ☐ HIV (AIDS)
- ☐ Sexually transmitted diseases
- ☐ Alcohol / Substance abuse
- ☐ Other: _____

Who will be allowed to release this information?

I authorize the following persons, groups or organizations to disclose the information described in this Release of Information/Authorization for the above referenced research study:

- ☒ **Treating providers**
- ☒ **Hospitals, clinics or other places where I have received treatment**
- ☐ **Other:**_____
- ☒ **The Principal Investigator and the Research Staff**

Who can access your PHI for the study? The people and entities listed above may share my PHI (or the PHI of the individual(s) whom I have the authority to represent), with the following persons or groups for the research study: the Research Team, IU Institutional Review Board and its designees, Research Sponsor and its representatives, Research Organizations, the Department of Health & Human Services or other US or foreign government agencies as required by law, and to the Food and Drug Administration (FDA) or a person subject to the jurisdiction of the FDA in order to audit or monitor the quality, safety or effectiveness of the product or activity.

The **Research Team** includes the Principal Investigator, his/her staff, research coordinators, research technicians and other staff members who provide assistance to the Research Team. If there is a **Research Sponsor(s),** this shall include: The National Institutes of Health and any **Research Organizations** who provided assistance to the **Research Sponsor(s)** including, but not limited to: RTI International (RTI), their data center.

INDIANA UNIVERSITY
AUTHORIZATION FOR THE RELEASE OF HEALTH INFORMATION FOR RESEARCH

Expiration date of this Authorization: This authorization is valid until the following date or event:

☐ Specify Date ___/___/____ ☐ End of the Study
☐ Other: _____ ☒ None; authorization is valid indefinitely

Efforts will be made to ensure that your PHI will not be shared with other people outside of the research study. However, your PHI may be disclosed to others as required by law and/or to individuals or organizations that oversee the conduct of research studies, and these individuals or organizations may not be held to the same legal privacy standards as are doctors and hospitals. Thus, the Research Team cannot guarantee absolute confidentiality and privacy.

I have the right:

1. To refuse to sign this form. Not signing the form will not affect my regular health care including treatment, payment, or enrollment in a health plan or eligibility for health care benefits. However, not signing the form will prevent me from participating in the research study above.

2. To review and obtain a copy of my personal health information collected during the study. However, it may be important to the success and integrity of the study that persons who participate in the study not be given access until the study is complete. The Principal Investigator has discretion to refuse to grant access to this information if it will affect the integrity of the study data during the course of the study. Therefore, my request for information may be delayed until the study is complete.

3. To cancel this release of information/authorization at any time. If I choose to cancel this release of information/authorization, I must notify the Principal Investigator for this study **in writing** at: Brenda Poindexter, MD, MS at 699 Riley Hospital Drive, RR208, Indianapolis, IN 46202. However, even if I cancel this release of information/authorization, the Research Team, Research Sponsor(s) and/or the Research Organizations may still use information about me that was collected as part of the research project between the date I signed the current form and the date I cancel the authorization. This is to protect the quality of the research results. I understand that canceling this authorization may end my participation in this study.

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_____
Printed name of Individual/Legal Representative

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Signature of Individual/Legal Representative *Date*

**If signed by a legal representative; state the relationship and identify below the authority to act on behalf of the individual's behalf.*

***Individual is:** ☒ a Minor ☐ Incompetent ☐ Disabled ☐ Deceased

***Legal Authority:**
☐ Custodial Parent ☐ Legal Guardian ☐ Executor of Estate of the Deceased
☐ Power of Attorney Healthcare ☐ Authorized Legal Representative
☐ Other: _____

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IRB REVIEWED
Oct. 24, 2012

INDIANA UNIVERSITY INFORMED CONSENT STATEMENT FOR

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

You and your baby are invited to participate in a study of blood transfusions (giving blood) in premature babies to better learn at which level of hemoglobin (this molecule carries oxygen) we should give blood to our babies so they might have better outcomes. Your baby qualifies because he/she was born early and has a high chance that they will receive at least one blood transfusion. We ask that you read this form and ask any questions you may have before agreeing to be in the study.

The study is being conducted by Dr. Brenda Poindexter from the Department of Pediatrics at Indiana University. It is funded by the National Institutes of Health (NIH), and sponsored by the National Institute of Child Health and Human Development (NICHD).

STUDY PURPOSE

The purpose of this study is to help doctors and nurses to better understand when we should give blood to our premature babies. Blood contains red cells, which carry a molecule called hemoglobin. Hemoglobin is necessary for life as it carries oxygen around the body. Hemoglobin is used by doctors as a measure of how many red blood cells are in your baby's body. Because premature babies need intensive care and cannot make red blood cells easily, they sometimes become anemic (where your body does not have enough healthy red blood cells and then can't provide enough oxygen to the body). Therefore, we have to give them blood. These blood transfusions are given when the hemoglobin falls below a certain level. It is routine to receive blood transfusions at hemoglobin levels based on your doctor's choice. We have found that some doctors tend to use the higher levels and some doctors tend to use the lower levels. This is because, at the moment, no one knows which level of hemoglobin is better. This study hopes to help us find out when we should best give blood to our babies.

NUMBER OF PEOPLE TAKING PART IN THE STUDY:

If you agree to participate, your baby will be one of 1824 babies from across the country who will also be participating in this research. Here, we will enroll about 100 babies.

PROCEDURES FOR THE STUDY:

The levels at which babies are being transfused in this study are well within the range at which doctors across the country routinely transfuse now, we are trying to establish what is the best level. This study is trying to give an answer to the question: "What is the best level of hemoglobin for transfusing babies?" If you agree that your baby can take part in this study, your baby will be randomly assigned (like a flip of a coin) to either the higher level of hemoglobin or the lower level. Both of these levels are in the usual range used by doctors in the NICU. The doctor will use this level of hemoglobin to decide when to transfuse the baby. If your baby was to get sick and immediately need a blood transfusion (when everyone would routinely give blood), your baby would get the blood no matter what the level of hemoglobin is/was.

All of the blood tests that are done are routine standard of care, ordered by your doctor, meaning this study does not ask for them. We will also ask you to complete a questionnaire that will help give us information as to how families cope with having a baby in the intensive care nursery.

Babies born this early are routinely seen in the Follow-up clinic when they are around 22 -26 months to check how well they are developing and growing. At this visit, they are observed playing with toys, how they walk, talk, and move around the room. We will also ask you to complete a short questionnaire about how your life and work schedule has been due to your baby's stay in the hospital.

RISKS OF TAKING PART IN THE STUDY:

While on the study, the risks are:

This study does not carry any extra risks to your baby if you choose to take part. There are no extra blood tests being done on your baby. This study does not change the care for your baby. The risks associated with this study are exactly the same risks that exist for your baby than any other baby who gets blood. Your baby's doctor will talk to you about this before giving blood. If your baby needs blood for emergency reasons, where all doctors would routinely give blood, they will get the blood they need – no matter what group they were in for the study. After that urgent need is over, they will then return to the study protocol.

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During the entire study, an independent committee will review this study to make sure that it continues to be safe.

The risks of completing the survey are being uncomfortable answering the questions and a possible loss of confidentiality.

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This study may not directly benefit your baby. However, your baby may benefit from additional monitoring during the study.

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Instead of being in the study, you could choose not to participate. The standard of care for your infant will not change.

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We will do our best to make sure that the personal information obtained during the course of this 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.

However, it is possible that other people may inspect and copy records pertaining to this research and this includes groups such as the federal government regulatory agencies, including the Office for Human Research Protections (OHRP), the U.S. Food and Drug Administration (FDA), The National Institute of Child Health and Human Development (NICHD), and its research designee (Research Triangle Institute-the data group) the NIH, and the study investigator, research associates and the Indiana University Institutional Review Board or its designees.

To help protect your and your baby's confidentiality, we will label information with a code number. The study logs linking the code number with your baby's identity will be kept in a locked office, in a locked file cabinet and on password-protected computer files. A copy of this Informed Consent Document will be placed in your and your baby's medical record and you will also get a copy.

A description of this clinical trial will be available on **ClinicalTrials.gov**, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

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CONTACTS FOR QUESTIONS OR PROBLEMS

For questions about the study or a research-related injury, contact Dr. Brenda Poindexter at 317-274-4768. If you cannot reach the researcher during regular business hours, and have questions about your rights being in research or to discuss problems or concerns, please call the IU Human Subjects Office at (317) 278-3458. After business hours, or in an emergency, please call the neonatologist on call at 317-948-4371.

For questions about your rights as a research participant or to discuss problems, complaints or concerns about a research study, or to obtain information, or offer input, contact the IU Human Subjects Office at (317) 278-3458.

VOLUNTARY NATURE OF STUDY

Taking part in this study is voluntary. You may choose for your baby not to take part or leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you or your baby are entitled. Your decision whether or not to participate in this study will not affect your current or future relations with Riley Hospital for Children at IU Health, Special Care Nursery at IU Health or Riley Hospital for Children at IU Health Methodist Hospital. We will tell you about new information that may affect your baby's health, welfare, or your willingness to allow your baby to stay in this study.

SUBJECT'S CONSENT

In consideration of all of the above, I give my consent for my baby to participate in this research study.

I will be given a copy of this informed consent document to keep for my records.

Baby's Printed Name:_____

Printed Name of Parent:_____

Signature of Parent:_____ Date:_____

Printed Name of Parent:_____

Signature of Parent:_____ Date:_____

Printed Name of Person Obtaining Consent:_____

Signature of Person Obtaining Consent:_____ **Date:**_____

For IRB Office Use ONLY

IRB Approval Date: Oct. 24, 2012
Expiration Date: Oct. 23, 2013

INFORMED CONSENT DOCUMENT

Project Title: **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?**

Principal Investigator: **Edward Bell, MD**

Research Team Contact: **Karen Johnson, RN (319)356-2924**
Edward Bell, MD (319)356-4006

This consent form describes the research study to help you decide if you want you and your baby to participate. This form provides important information about what you and your baby will be asked to do during the study, about the risks and benefits of the study, and about your rights as a research subjects.

- If you have any questions about or do not understand something in this form, you should ask the research team for more information.
- You should discuss your participation and your baby's participation with anyone you choose such as family or friends.
- Do not agree to for you and your baby participate in this study unless the research team has answered your questions and you decide that you want to be part of this study.

WHAT IS THE PURPOSE OF THIS STUDY?

This is a research study. We are inviting you and your baby to participate in this research study because your baby was born weighing less than or equal to 1,000 grams (about 2 pounds 4 ounces) and/or between 22 and 29 weeks gestational age at birth.

The purpose of this research study is to gather information to understand when we should transfuse blood (as red cells) into the blood of premature infants. Blood contains red cells, which carry a molecule called hemoglobin. Hemoglobin is necessary for life and carries oxygen around the body. It can be measured, and is used by doctors as a measure of how many red blood cells are circulating in your baby's body.

Premature babies need a lot of blood tests to monitor their care. Doctors try their best to order only a few blood tests depending on the needs of the premature babies. Since premature infants cannot make red blood cells easily, they sometimes become anemic.

When the hemoglobin falls below a certain level, a blood transfusion is given to the baby. Some doctors tend to use a higher level of hemoglobin and some doctors tend to use a lower level of hemoglobin. The reason for this is that we do not know which level of hemoglobin is better. This study aims to help us find out when we should best transfuse babies.

HOW MANY PEOPLE WILL PARTICIPATE?

Approximately 100 mother-baby pairs will take part in this study conducted by investigators at the University of Iowa. Approximately 1,824 mother-baby pairs will take part nationwide.

HOW LONG WILL I BE IN THIS STUDY?

If you agree to take part in this study, your involvement and your baby's involvement will last for 2 years, including while your baby is a patient in the NICU and at a follow-up visit when your baby is between 22 and 26 months old.

WHAT WILL HAPPEN DURING THIS STUDY?

If you agree that you and your baby should take part in this study, your baby will be randomly assigned (like a flip of a coin) to either the higher level of hemoglobin or the lower level. Both of these levels are in the usual range used by doctors in the NICU. The doctor will use this level of hemoglobin to decide when to transfuse your baby. If your baby were to get unexpectedly ill or have an unexpected urgent need for blood transfusion, your baby would get the transfusion regardless of the level of hemoglobin. Blood transfusions will be given into a vein, the same way all transfusions are given to babies. Your baby's doctor will also ask you to sign a "consent for blood transfusions", whether or not your baby is in the study.

During the in-hospital study period, we will measure your baby's head circumference weekly.
All of the blood tests that are done are routine standard of care. We will retrieve any blood leftover from these tests. These leftover blood samples will be taken to a research laboratory and analyzed for markers of inflammation, which may be a result of transfusion. We will also place a cotton pad in your baby's diaper once a week to collect urine, which will also be sent to the research laboratory to be analyzed for markers of inflammation.

Before your baby is discharged, we will ask you to complete an economic questionnaire that will help provide us with information as to how families cope with having a baby in the intensive care nursery. We will also ask you questions about your household, your education level, whether you are working, and your insurance. You are free to skip any questions that you prefer not to answer.

We will arrange for you and your baby to come back for a 22-26 month follow-up appointment in the Pediatric Specialty Clinic. At this visit, a trained nurse practitioner will collect information about your household, your education level, your insurance, and your baby's medical history since discharge. You will also be asked to answer questions about the type of help you may have used since your baby was discharged to help us calculate the costs of care. You are free to skip any questions that you prefer not to answer. The nurse practitioner will also perform a physical and neurological exam and developmental testing. The visit will last between 1 and 1 ½ hours.

Sometimes families change their address and or telephone number. To ensure that we have a way of reaching you, we will collect your address, phone number, and email address, as well as those of someone else we could contact if we cannot find you. We might also use social media, or call your baby's doctor's office if needed to find you.

We will collect information from your medical record and your baby's medical record. The information we will collect about you includes your age, marital status, level of education, medical insurance, race, ethnicity, pregnancy, labor and delivery, and medications you were given during pregnancy. The information we will collect about your baby includes his/her treatments, diagnoses and outcomes while hospitalized.

SOCIAL SECURITY NUMBER (SSN) USAGE

You will be asked to provide your social security number or your baby's social security number on a form that will be given to you at discharge. The collection of your social security number is to be sent to the UI business office so they may send you a reimbursement check after the follow-up visit. In case we lose contact with you in the future, we may also use your and your baby's social security number to attempt to locate you for scheduling the follow-up visit. The collection of your social security number, **for research purposes other than payment**, is strictly optional and is not required for participation in the study.

____ I allow you to collect and use my social security number for the purposes outlined above.

____ I do NOT allow you to collect or use my social security number for the purposes outlined above. (Initial your choice above)

WHAT ARE THE RISKS OF THIS STUDY?

You and your baby may experience one or more of the risks indicated below from being in this study. In addition to these, there may be other unknown risks, or risks that we did not anticipate, associated with being in this study.

Blood transfusions are in general extremely safe. Giving blood transfusions at too high a hemoglobin level may result not only in more blood transfusions, but the babies may take longer to mature their own bone marrow to produce their own blood. On the other hand, transfusing at too low a hemoglobin level, could lead to the baby not having enough hemoglobin to carry enough oxygen around the body. We avoid these extremes by transfusing within the ranges of hemoglobin level that doctors already use. Some of the questions we will ask you for the study might make you feel uncomfortable. You may choose not to answer any questions you wish.

WHAT ARE THE BENEFITS OF THIS STUDY?

We don't know if you and your baby will benefit from being in this study.

However, we hope that, in the future, other people might benefit from this study because we will know when it is best to give a transfusion.

WHAT OTHER TREATMENT OPTIONS ARE THERE?

Before you decide whether or not to be in this study, your doctor will discuss the other options that are available to you. Instead of being in this study, you could choose for you and your baby to not participate. Then, each of your baby's doctors would decide when he/she will be given a transfusion.

WILL IT COST ME ANYTHING TO BE IN THIS STUDY?

You will not have any additional costs for being in this research study.
You and/or your medical/hospital insurance carrier will remain responsible for your and your baby's regular medical care expenses.

WILL I BE PAID FOR PARTICIPATING?

You will be paid for being in this research study. You will need to provide your social security number (SSN) in order for us to pay you. You may choose to participate without being paid if you do not wish to provide your social security number (SSN) for this purpose. You may also need to provide your address so a check can be mailed to you. If your social security number is obtained for payment purposes only, it will not be retained for research purposes, unless you give permission.

You will be paid $50 after the follow-up visit and will be given parking vouchers at the follow-up visit.

WHO IS FUNDING THIS STUDY?

The NICHD (National Institute of Child Health and Human Development) Neonatal Research Network, part of the National Institutes of Health (NIH) is funding this research study. This means that the University of Iowa is receiving payments from the NICHD Neonatal Research Network to support the activities that are required to conduct the study. No one on the research team will receive a direct payment or increase in salary from the NICHD Neonatal Research Network for conducting this study.

WHAT IF MY BABY IS INJURED AS A RESULT OF THIS STUDY?

- If your baby is injured or becomes ill from taking part in this study, medical treatment is available at the University of Iowa Hospitals and Clinics.
- The University of Iowa does not plan to provide free medical care or payment for treatment of any illness or injury resulting from this study unless it is the direct result of proven negligence by a University employee.
- If your baby experiences a research-related illness or injury, you and/or your medical or hospital insurance carrier will be responsible for the cost of treatment.

WHAT ABOUT CONFIDENTIALITY?

We will keep your participation and your baby's participation in this research study confidential to the extent permitted by law. However, it is possible that other people such as those indicated below may become aware of your participation and your baby's participation in this study and may inspect and copy records pertaining to this research. Some of these records could contain information that personally identifies you or your baby.

- federal government regulatory agencies,
- The National Institutes of Health Neonatal Research Network;
- Research Triangle Institute (the organization that will analyze the data);
- auditing departments of the University of Iowa, and

- the University of Iowa Institutional Review Board (a committee that reviews and approves research studies)

To help protect your confidentiality and your baby's confidentiality, we will use a code number on all data forms. The study log linking the code number with your identity and your baby's identity will be kept in a locked office, in a locked file cabinet and on password-protected computer files. If we write a report or article about this study or share the study data set with others, we will do so in such a way that you cannot be directly identified.

The University of Iowa Hospitals and Clinics generally requires that we document in your baby's medical record chart that he/she is participating in this study. The information included in the chart will provide contact information for the research team as well as information about the risks associated with this study. We will keep this Informed Consent Document in our research files; it will not be placed in your baby's medical record chart.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, identifier: NCT 01702805 as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

WILL MY HEALTH INFORMATION BE USED DURING THIS STUDY?

The Federal Health Insurance Portability and Accountability Act (HIPAA) requires University of Iowa Health Care to obtain your permission for the research team to access or create "protected health information" about you and your baby for purposes of this research study. Protected health information is information that personally identifies you and your baby and relates to your and your baby's past, present, or future physical or mental health condition or care. We will access or create health information about you and your baby, as described in this document, for purposes of this research study and for your treatment. Once University of Iowa Health Care has disclosed your and your baby's protected health information to us, it may no longer be protected by the Federal HIPAA privacy regulations, but we will continue to protect your and your baby's confidentiality as described under "Confidentiality."

We may share your and your baby's health information related to this study with other parties including federal government regulatory agencies, the University of Iowa Institutional Review Boards and support staff, the NICHD Neonatal Research Network, and Research Triangle Institute (the organization that will analyze the data). The sponsor, NICHD Neonatal Research Network may also inspect any part of your and your baby's medical record for the purposes of auditing the conduct of the study.

You and your baby cannot participate in this study unless you permit us to use your and your baby's protected health information. If you choose *not* to allow us to use your and your baby's protected health information, we will discuss any non-research alternatives available to you. Your decision will not affect your or your baby's right to medical care that is not research-related. Your signature on this Consent Document authorizes University of Iowa Health Care to give us permission to use or create health information about you and your baby.

Although you may not be allowed to see study information until after this study is over, you may be given access to your and your baby's health care records by contacting your health care provider. Your permission for us to access or create protected health information about you and your baby for purposes of this study has no expiration date. You may withdraw your permission for us to use your and your baby's health information for this research study by sending a written notice to Dr. Edward Bell, University of Iowa Hospitals & Clinics, 200 Hawkins Dr., Dept. of Pediatrics, 8811 JPP, Iowa City, Iowa 52242. However, we may still use your and your baby's health information that was collected before withdrawing your permission. Also, if we have sent your and your baby's health information to a third party, such as the study sponsor, or we have removed your or your baby's identifying information, it may not be possible to prevent its future use. You will receive a copy of this signed document.

IS BEING IN THIS STUDY VOLUNTARY?

Taking part in this research study is completely voluntary. You may choose for you and your baby not to take part at all. If you decide for you and your baby to be in this study, you may stop participating at any time. If you decide not to be in this study, or if you stop participating at any time, you and your baby won't be penalized or lose any benefits for which you and your baby otherwise qualify.

What if I Decide to Drop Out of the Study?

If you decide to leave or withdraw your baby from the study early, your baby's clinical physician will decide when to give further transfusion, but we will ask you to return for the 22-26 month follow up visit if possible.

Will I Receive New Information About the Study while Participating?

If we obtain any new information during this study that might affect your willingness to continue participating in the study, we'll promptly provide you with that information.

Can Someone Else End my Participation in this Study?

Under certain circumstances, the researchers might decide to end your baby's participation in this research study earlier than planned. This might happen if, in our judgment, it would not be safe for your baby to continue, because funding for the research study has ended, or because the NICHD Neonatal Research Network has decided to stop the study.

WHAT IF I HAVE QUESTIONS?

We encourage you to ask questions. If you have any questions about the research study itself, please contact: Dr. Edward Bell at 319-356-4006 or Karen Johnson, R.N. at 319-356-2924. If your baby experiences a research-related injury, please contact: Dr. Edward Bell at 319-356-4006, or call 319-356-1616 and ask the operator to page Dr. Bell or the neonatologist on call.

If you have questions, concerns, or complaints about your rights as a research subject or about research related injury, please contact the Human Subjects Office, 105 Hardin Library for the Health Sciences, 600 Newton Rd, The University of Iowa, Iowa City, IA 52242-1098, (319) 335-6564, or e-mail irb@uiowa.edu. General information about being a research subject can be found by clicking "Info for Public" on the Human Subjects Office web site, http://hso.research.uiowa.edu/. To offer input about your experiences as a research subject or to speak to someone other than the research staff, call the Human Subjects Office at the number above.

This Informed Consent Document is not a contract. It is a written explanation of what will happen during the study if you decide to participate. You are not waiving any legal rights by signing this Informed Consent Document. Your signature indicates that this research study has been explained to you, that your questions have been answered, and that you agree to take part in this study. You will receive a copy of this form.

Subject's Name - mother (printed):

_____

Subject's Name – infant (printed):

_____

Parent/Guardian's Name and Relationship to Subject:

_____ _____
(Name – printed) (Relationship to subject – printed)

Do not sign this form if today's date is on or after EXPIRATION DATE: 12/13/13.

_____ _____
(Signature of Parent/Guardian) (Date)
(Signature of Mother – subject)

Statement of Person Who Obtained Consent

I have discussed the above points with the subject or, where appropriate, with the subject's legally authorized representative. It is my opinion that the subject understands the risks, benefits, and procedures involved with participation in this research study.

_____ _____
(Signature of Person who Obtained Consent) (Date)

INFORMED CONSENT DOCUMENT

Project Title: **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?**

Principal Investigator: **Edward Bell, MD**

Research Team Contact: **Karen Johnson, RN (319)356-2924**
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However, we hope that, in the future, other people might benefit from this study because we will know when it is best to give a transfusion.

WHAT OTHER TREATMENT OPTIONS ARE THERE?

Before you decide whether or not to be in this study, your doctor will discuss the other options that are available to you. Instead of being in this study, you could choose for you and your baby to not participate. Then, each of your baby's doctors would decide when he/she will be given a transfusion.

WILL IT COST ME ANYTHING TO BE IN THIS STUDY?

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You and/or your medical/hospital insurance carrier will remain responsible for your and your baby's regular medical care expenses.

WILL I BE PAID FOR PARTICIPATING?

You will be paid for being in this research study. You will need to provide your social security number (SSN) in order for us to pay you. You may choose to participate without being paid if you do not wish to provide your social security number (SSN) for this purpose. You may also need to provide your address so a check can be mailed to you. If your social security number is obtained for payment purposes only, it will not be retained for research purposes, unless you give permission.

You will be paid $50 after the follow-up visit and will be given parking vouchers at the follow-up visit.

WHO IS FUNDING THIS STUDY?

The NICHD (National Institute of Child Health and Human Development) Neonatal Research Network, part of the National Institutes of Health (NIH) is funding this research study. This means that the University of Iowa is receiving payments from the NICHD Neonatal Research Network to support the activities that are required to conduct the study. No one on the research team will receive a direct payment or increase in salary from the NICHD Neonatal Research Network for conducting this study.

WHAT IF MY BABY IS INJURED AS A RESULT OF THIS STUDY?

- If your baby is injured or becomes ill from taking part in this study, medical treatment is available at the University of Iowa Hospitals and Clinics.
- The University of Iowa does not plan to provide free medical care or payment for treatment of any illness or injury resulting from this study unless it is the direct result of proven negligence by a University employee.
- If your baby experiences a research-related illness or injury, you and/or your medical or hospital insurance carrier will be responsible for the cost of treatment.

WHAT ABOUT CONFIDENTIALITY?

We will keep your participation and your baby's participation in this research study confidential to the extent permitted by law. However, it is possible that other people such as those indicated below may become aware of your participation and your baby's participation in this study and may inspect and copy records pertaining to this research. Some of these records could contain information that personally identifies you or your baby.

- federal government regulatory agencies,
- The National Institutes of Health Neonatal Research Network;
- Research Triangle Institute (the organization that will analyze the data);
- auditing departments of the University of Iowa, and
- the University of Iowa Institutional Review Board (a committee that reviews and approves research studies)

To help protect your confidentiality and your baby's confidentiality, we will use a code number on all data forms. The study log linking the code number with your identity and your baby's identity will be kept in a locked office, in a locked file cabinet and on password-protected computer files. If we write a report or article about this study or share the study data set with others, we will do so in such a way that you cannot be directly identified.

The University of Iowa Hospitals and Clinics generally requires that we document in your baby's medical record chart that he/she is participating in this study. The information included in the chart will provide contact information for the research team as well as information about the risks associated with this study. We will keep this Informed Consent Document in our research files; it will not be placed in your baby's medical record chart.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, identifier: NCT 01702805 as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

WILL MY HEALTH INFORMATION BE USED DURING THIS STUDY?

The Federal Health Insurance Portability and Accountability Act (HIPAA) requires University of Iowa Health Care to obtain your permission for the research team to access or create "protected health information" about you and your baby for purposes of this research study. Protected health information is information that personally identifies you and your baby and relates to your and your baby's past, present, or future physical or mental health condition or care. We will access or create health information about you and your baby, as described in this document, for purposes of this research study and for your treatment. Once University of Iowa Health Care has disclosed your and your baby's protected health information to us, it may no longer be protected by the Federal HIPAA privacy regulations, but we will continue to protect your and your baby's confidentiality as described under "Confidentiality."

We may share your and your baby's health information related to this study with other parties including federal government regulatory agencies, the University of Iowa Institutional Review Boards and support staff, the NICHD Neonatal Research Network, and Research Triangle Institute (the organization that will analyze the data). The sponsor, NICHD Neonatal Research Network may also inspect any part of your and your baby's medical record for the purposes of auditing the conduct of the study.

You and your baby cannot participate in this study unless you permit us to use your and your baby's protected health information. If you choose *not* to allow us to use your and your baby's protected health information, we will discuss any non-research alternatives available to you. Your decision will not affect your or your baby's right to medical care that is not research-related. Your signature on this Consent Document authorizes University of Iowa Health Care to give us permission to use or create health information about you and your baby.

Although you may not be allowed to see study information until after this study is over, you may be given access to your and your baby's health care records by contacting your health care provider. Your permission for us to access or create protected health information about you and your baby for purposes of this study has no expiration date. You may withdraw your permission for us to use your and your

baby's health information for this research study by sending a written notice to Dr. Edward Bell, University of Iowa Hospitals & Clinics, 200 Hawkins Dr., Dept. of Pediatrics, 8811 JPP, Iowa City, Iowa 52242. However, we may still use your and your baby's health information that was collected before withdrawing your permission. Also, if we have sent your and your baby's health information to a third party, such as the study sponsor, or we have removed your or your baby's identifying information, it may not be possible to prevent its future use. You will receive a copy of this signed document.

IS BEING IN THIS STUDY VOLUNTARY?

Taking part in this research study is completely voluntary. You may choose for you and your baby not to take part at all. If you decide for you and your baby to be in this study, you may stop participating at any time. If you decide not to be in this study, or if you stop participating at any time, you and your baby won't be penalized or lose any benefits for which you and your baby otherwise qualify.

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If you decide to leave or withdraw your baby from the study early, your baby's clinical physician will decide when to give further transfusion, but we will ask you to return for the 22-26 month follow up visit if possible.

Will I Receive New Information About the Study while Participating?

If we obtain any new information during this study that might affect your willingness to continue participating in the study, we'll promptly provide you with that information.

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Under certain circumstances, the researchers might decide to end your baby's participation in this research study earlier than planned. This might happen if, in our judgment, it would not be safe for your baby to continue, because funding for the research study has ended, or because the NICHD Neonatal Research Network has decided to stop the study.

WHAT IF I HAVE QUESTIONS?

We encourage you to ask questions. If you have any questions about the research study itself, please contact: Dr. Edward Bell at 319-356-4006 or Karen Johnson, R.N. at 319-356-2924. If your baby experiences a research-related injury, please contact: Dr. Edward Bell at 319-356-4006, or call 319-356-1616 and ask the operator to page Dr. Bell or the neonatologist on call.

If you have questions, concerns, or complaints about your rights as a research subject or about research related injury, please contact the Human Subjects Office, 105 Hardin Library for the Health Sciences, 600 Newton Rd, The University of Iowa, Iowa City, IA 52242-1098, (319) 335-6564, or e-mail irb@uiowa.edu. General information about being a research subject can be found by clicking "Info for Public" on the Human Subjects Office web site, http://hso.research.uiowa.edu/. To offer input about your experiences as a research subject or to speak to someone other than the research staff, call the Human Subjects Office at the number above.

This Informed Consent Document is not a contract. It is a written explanation of what will happen during the study if you decide to participate. You are not waiving any legal rights by signing this Informed Consent Document. Your signature indicates that this research study has been explained to you, that your questions have been answered, and that you agree to take part in this study. You will receive a copy of this form.

Subject's Name - mother (printed):

_____

Subject's Name – infant (printed):

_____

Parent/Guardian's Name and Relationship to Subject:

_____ _____

(Name – printed) (Relationship to subject – printed)

Do not sign this form if today's date is on or after EXPIRATION DATE: 12/13/13.

_____ _____

(Signature of Parent/Guardian) (Date)
(Signature of Mother – subject)

Statement of Person Who Obtained Consent

I have discussed the above points with the subject or, where appropriate, with the subject's legally authorized representative. It is my opinion that the subject understands the risks, benefits, and procedures involved with participation in this research study.

_____ _____

(Signature of Person who Obtained Consent) (Date)

THE UNIVERSITY OF IOWA

Human Subjects Office/
Institutional Review Board (IRB)
105 Hardin Library for the Health Sciences
600 Newton Road
Iowa City, Iowa 52242-1098
319-335-6564 *Fax* 319-335-7310
irb@uiowa.edu
http://research.uiowa.edu/hso

IRB ID #: 201211720

To: Edward Bell

From: IRB-01 Univ of Iowa DHHS Registration # IRB00000099, DHHS Federalwide Assurance # FWA00003007

Re: 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?

Protocol Number:
Protocol Version: 1.0
Protocol Date: 10/8/12
Amendment Number/Date(s):

Approval Date: 12/18/12 (Full Board)

This project has been granted a partial waiver of HIPAA Authorization based on the documentation provided by the researcher in the HawkIRB application Section VII.D and the assurance document signed by the Principal Investigator.

This partial waiver of authorization for recruitment purposes satisfies the following criteria:
(1) The use or disclosure of the requested information involves no more than a minimal risk to the privacy of individuals based on, at least, the presence of the following elements:
(a) An adequate plan to protect the identifiers from improper use and disclosure
(b) An adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law; and
(c) Adequate written assurances that the requested information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of the requested information would be permitted by the Privacy Rule;
(2) The research could not practicably be conducted without the waiver or alteration; and
(3) The research could not practicably be conducted without access to and use of the requested information.

This approval has been electronically signed by IRB Chair:
Herbert Berger, MD, MD
12/18/12 1837

THE UNIVERSITY OF IOWA

Human Subjects Office/
Institutional Review Board (IRB)
105 Hardin Library for the Health Sciences
600 Newton Road
Iowa City, Iowa 52242-1098
319-335-6564 *Fax* 319-335-7310
irb@uiowa.edu
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Protocol Number:
Protocol Version: 1.0
Protocol Date: 10/8/12
Amendment Number/Date(s):

Approval Date: 12/18/12 (Full Board)

This project has been granted a full waiver of HIPAA Authorization based on the documentation provided by the researcher in the HawkIRB application Section IV and the assurance document signed by the Principal Investigator.

This full waiver of authorization satisfies the following criteria:
(1) The use or disclosure of the requested information involves no more than a minimal risk to the privacy of individuals based on, at least, the presence of the following elements:
(a) An adequate plan to protect the identifiers from improper use and disclosure
(b) An adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law; and
(c) Adequate written assurances that the requested information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of the requested information would be permitted by the Privacy Rule;
(2) The research could not practicably be conducted without the waiver or alteration; and
(3) The research could not practicably be conducted without access to and use of the requested information.

This approval has been electronically signed by IRB Chair:
Herbert Berger, MD, MD
12/18/12 1837

CONSENT TO PARTICIPATE IN A MEDICAL RESEARCH STUDY

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?

Transfusion of Prematures - TOP

This document describes a research study for which your baby may be eligible. It is designed to provide information you will need to decide if you want your baby to participate. This form includes information about what will happen during the study, the risks and benefits of the research and the rights of research participants.

- If you have questions about this research or if there is something you do not understand, you should ask a member of the research team.
- You should discuss your participation with family or friends if you choose.
- You should not sign this consent form unless you have had all of your questions satisfactorily answered by the research team.

Why is this study being done?

We are inviting you and your baby to participate in this research study because your baby was born weighing less than or equal to 1,000grams (about 2 pounds 4 ounces) and between 22 and 29 weeks gestational age at birth.

The purpose of this research study is to gather information to understand when we should transfuse blood (provide more red blood cells through an IV) into the blood of premature infants. Blood contains red cells, which carry a molecule called hemoglobin. Hemoglobin is necessary for life and carries oxygen around the body. It can be measured, and is used by doctors as a measure of how many red blood cells are circulating in your baby's body.

Premature babies need a lot of blood tests to monitor their care. Doctors try their best to order only a few blood tests depending on the needs of the premature babies. Since premature infants cannot make red blood cells easily, they sometimes become anemic (or low on their red blood cell count).

When the hemoglobin falls below a certain level, a blood transfusion is given to the baby. Some doctors tend to use a higher level of hemoglobin and some doctors use a lower level of hemoglobin to decide when to give a blood transfusion to babies. The reason for this is because we do not know which approach is better. This study will help us to find out the best timing to provide blood transfusions to babies.

Who is on the research team?

The research team includes Dr. Dan Ellsbury who serves as the project director at the Mercy NICU. He is assisted by Donia Campbell, R.N.C., who is the Research Coordinator at the Mercy Medical Center NICU. Research nurse Brianna Damstetter, R.N.C. and Dr. Cary Murphy are also part of this study team. The research is being conducted in collaboration with the University of Iowa and Dr. Edward Bell is the overall project director for this study at the University of Iowa and Mercy Medical Center NICU.

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How many people will participate?

Approximately 100 mother-baby pairs will take part in this study conducted here at the Mercy Medical Center NICU. About 1,824 mother-baby pairs will take part nationwide in over 18 different centers.

How long will my baby be in this study?

If you agree to take part in this study, your involvement and your baby's involvement will last for 2 years, including while your baby is a patient in the NICU and at a follow up visit when your baby is between 22 and 26 months of age here at Mercy Medical Center in the Research office with members of the Iowa City High Risk Infant Follow Up Team. The visit may take around 1-2 hours.

What will happen during this study?

If you agree for you and your baby to participate in this study, your baby will be randomly assigned (like a flip of a coin) to either the higher level of hemoglobin or the lower level group. Both of these levels are in the usual range used by doctors in the NICU. The doctor will use this level of hemoglobin to decide when to transfuse your baby. If your baby were to get unexpectedly ill or have an unexpected urgent need for a blood transfusion, your baby will get a transfusion, regardless of the level of hemoglobin. Blood transfusions will be given into a vein through an IV placed by your baby's nurse, or by a special IV access into your baby's umbilical cord which is commonly placed by the doctor shortly after birth in extremely preterm babies. This is how transfusions are given to all babies. You will be asked to sign a "Consent to Transfuse Blood" whether your baby is in the study or not.

During your baby's hospital stay, we will be measuring your baby's head circumference. This measurement is already being done weekly and recorded by NICU nursing staff. All of the blood tests being done are already part of your baby's routine care.

Before your baby is discharged, we will ask you to complete an economic questionnaire that will help provide us with information as to how families cope with having a baby in the intensive care nursery. We will also ask you questions about your household, your education level, whether you are working, and your insurance. You are free to skip any questions that you prefer not to answer.

We will arrange for you and your baby to come back for a 22-26 month follow up appointment in the Research Office located just outside the Mercy Medical Center NICU. At this visit a trained nurse practitioner will collect information about your household, your education level, your insurance, and your baby's medical history since discharge. You are free to skip any questions that you prefer not to answer. We will also ask you to complete another economic questionnaire, similar to the one that was completed during your baby's hospital stay. The nurse practitioner will also perform a physical and neurological exam as well as a developmental evaluation. This visit may take up to 1-2 hours and while this sounds like a long visit, the children at this age do quite well. Your child will be provided breaks if necessary during the visit.

Some families change their address and or telephone numbers. To ensure that we have a way of reaching you, we will collect your address, phone number, and email address, as well as those of someone else we could contact if we cannot find you. We may also utilize social media (such as Facebook, etc.) or known doctor's offices in order to locate updated information in order to reach you to schedule the visit.

We will be collecting information from your medical record and your baby's medical record. The information we will collect about you includes your age, marital status, level of education, medical insurance, race, ethnicity, pregnancy, labor and delivery, and any medications you were on during your pregnancy. The information we will collect about your baby includes his/her treatments, diagnoses and outcomes while he/she was hospitalized in the NICU.

What are the risks of the study?

You and your baby may experience one or more of the risks indicated below from being in this study. In addition to these, there may be other unknown risks, or risks that we did not anticipate, associated with being in this study.

As described above, blood is often given to the baby through an IV in a vein. Sometimes the IV that was placed in a vein may leak into the baby's skin during the blood transfusion and might cause a bruise. We monitor the IV site closely during the transfusion. If this should happen, we will stop the blood and place a new IV. To prevent this from happening, we attempt to use new IV sites if possible, while at the same time taking caution not to replace IV sites when not necessary for your baby's comfort.

Blood transfusions are in general extremely safe. Giving blood transfusions at too high a hemoglobin level may result not only in more blood transfusions, but the babies may take longer to mature their own bone marrow to produce their own blood. On the other hand, transfusing at too low a hemoglobin level, could lead to the baby not having enough hemoglobin to carry enough oxygen around the body. We avoid these extremes by transfusing blood cells within the ranges of the hemoglobin levels that doctors already use.

We may ask questions privately for questionnaires, if any of the questions should make you uncomfortable, you may choose not to answer.

What are the benefits of this study?

We do not know if you and your baby will benefit from being in this study. However, we hope that, in the future, other people might benefit from this study because we will know when it is best to give blood transfusions to babies.

Will it cost me anything to be in this study?

No, you will not have any additional costs for being in this study. The cost of you and your baby's regular medical expenses will remain the responsibility of you and/or your medical/hospital insurance carrier.

What if my baby is injured as a result of the study?

If your baby is injured or becomes ill from taking part in this study, medical treatment is available at Mercy Medical Center NICU. Mercy Medical Center does not provide free medical care or payment for treatment of any illness or injury resulting from this study unless it is the direct result of proven negligence by an employee. If your baby experiences a research related illness or injury, your and/or your medical or hospital insurance carrier will be responsible for the cost of treatment.

Will I be paid for participating?

You will not be paid for being in this research study, but we do understand that you may experience additional costs when you bring your baby back for his/her 22-26 month follow up examination. The study will provide $50 to you after the follow up visit in order to help with these expenses. ***In order to pay you, we will need to***

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collect your social security number at the time of your visit. You will also need to provide an address to which we may mail the check.

Sometimes families change addresses or phone numbers and to be sure that we have another way of reaching you we ask that we be able to collect your social security number and your baby's social security number which will be kept in a locked file cabinet for the sole use of the research team. Besides reimbursement for your follow up visit, the social security number will help us locate you if we lose contact with you in the future. ***The use of your social security numbers for research purposes other than for payment is strictly optional.***

__ I allow you to collect my social security number for the purposes described above

__ I DO NOT allow you to collect my social security number for the purposes described above

We would like to keep in contact with you and your baby beyond the follow up visit in case the study analysis shows a need for additional follow up. Agreeing to be in this study does not obligate you and your baby to be in future studies. If we decide to have an additional study in the future we will ask you to sign a separate consent for that study.

Who is funding this study?

The cost of the research is being funded in part by the National Institutes of Health Neonatal Research Network and some funding has been provided by the Pediatrix Corporation to support the cost of a research nurse. None of the investigators are personally receiving funds from this study, nor are their salaries being supported by the research grant. This study is being conducted by the National Institute of Child Health and Human Development Neonatal Research Network. This trial is registered in the NIH ClinicalTrials.gov registry (www.ClinicalTrials.gov) under record number 01702805 as required by U.S. Law. A description of the trial may be found there. The website is open to the public and you may see it at any time. This website will not include information that would identify you or your baby.

What about confidentiality?

We will keep your participation confidential to the fullest extent permitted by law. However, it is possible that other people may become aware of your participation. Federal government regulatory agencies, financial accounting personnel of Mercy Medical Center, members of ethics panels (Institutional Review Board – a committee that reviews and approves research studies) may review records that personally identify you. Research staff from the University of Iowa (who are partnering in this research) may review records for accuracy and data quality. Information about your baby in a form that is not personally identifiable will be transmitted to Research Triangle Institute, the agency managing data for this study.

To help protect your confidentiality, we use code numbers on all data forms. The document linking your identity to the code number will be kept in a locked office in a locked file cabinet at Mercy Medical Center and any electronic files will be kept on password protected computers in encrypted files. Whenever this data is used in writing a research report the data will be combined with other patients' data and the report will be presented in a manner that does not personally identify you or your baby.

Will my health information be used during this study?

The Federal Health Insurance Portability and Accountability Act (HIPAA) require Mercy Medical Center to obtain your permission to allow the research team to access and use "protected health information" (information that personally identifies you or your baby and relates to past, present or future physical or mental health condition or care). We will access or create health information about you or your baby as

described in this document, for purposes of this research study. Once Mercy Medical Center has disclosed your protected health information to the research team, that information may no longer be protected by the Federal HIPAA privacy regulations, but we will still continue to protect your confidentiality.

We may share health information pertaining to you and your baby with other parties including Federal government regulatory agencies, the Mercy Medical Center Institutional Review Board and its support staff and the NICHD Neonatal Research Network or staff of the Research Triangle Institute which provide data management service for the NICHD.

Although you may not be allowed to see study information until after the study is over, you may be given access to health care records for you and your baby by contacting your health care provider. Your permission for us to access or create protected health information pertaining to you and your baby has no expiration date, but if you want to withdraw your permission for our use of protected health information you may do so by informing the Research Team at 515-358-4088 where you will reach the NICU research nurses. You may also contact Dr. Dan Ellsbury the project director at Mercy Medical Center NICU 515-358-4000 (Mercy Medical Center NICU, 1111 6th Avenue, Des Moines, Iowa 50314). Information collected before your withdrawal may still be used and it might not be possible to prevent future use of any information already disclosed to a third party.

What if I choose not to participate?

You and your baby cannot participate in this research study unless you authorize us to use your protected health information, which includes your social security number in order to pay you after the follow up is completed.

You do not have to participate in this research study.

If you choose not to participate you will receive the same care as if you were participating in the study and no loss of benefits to which you are otherwise entitled can be withdrawn.

Do I have to be in this study?

Taking part in this study is completely voluntary. You may choose not to take part at all in this study. If you decide to be in this study you may stop participating at any time. If you decide to stop participating in this study you will not be penalized or lose any benefits for which you or your baby otherwise qualify.

Will I receive New Information About the Study while Participating?

If we obtain any new information during this study that might affect your willingness to continue participating in the study, we will promptly provide you with that information.

Can Someone Else End my Participation in this Study?

Under certain circumstances, the researchers might decide to end your baby's participation in this research study earlier than planned. This might happen if, in our judgment, it would not be safe for your baby to continue, because funding for the research study has ended, or because the NICHD Neonatal Research Network has decided to stop the study.

What other Treatment Options are there?

Before you decide whether or not to be in this study, your doctor will discuss the other options that are available to you. Instead of being in this study, you could choose for you and your baby to not participate. Each of your baby's doctors would then decide when he/she will be given a blood transfusion.

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Who can I contact if I have questions?

For questions about participating in this study, please contact your NICU research coordinator first. You may call Donia Campbell, R.N.C. and Brianna Damstetter, R.N.C. at 515-358-4000 or 515-358-4088. You may also call the principal investigator, Dr. Dan Ellsbury at 515-262-3916. If you have questions about your rights and responsibilities as a participant in a research study you may contact the chairpersons of either the Mercy Medical Center Institutional Review Board, Dr. Matt Andres 515-247-3985. If you have questions about the confidentiality of your medical information you may call the Mercy Medical Center Privacy officer at 515-643-4557.

Patient's Consent: TRANSFUSION OF PREMATURES STUDY

- I understand that I can refuse to participate in this research project.
- I understand that I can withdraw my consent and discontinue participation in the project at any time without penalty or loss of benefits to which I am otherwise entitled.
- My refusal will not affect my relationship with the institution involved in the research project.
- My signature below indicates that all of my questions have been answered to my satisfaction and in a language that I understand.
- I agree to participate in the project as described above.
- I understand that I will be given a signed copy of this form for my personal records.
- I acknowledge that the committee or governing review board including Mercy Medical Center Institutional Review Board or any other governing agency or organization may access my study records or other medical records as allowed by law.
- I understand that I am not waiving any of my legal rights.

A signed copy of this form will be given to you.

Child's name (printed)_____

Mother's name (printed)_____

Signature of mother_____ **Date**_____

Parent/Guardian or Legally Authorized Representative's Name and Relationship to Subject:

Guardian Name (printed)_____ **Relationship to Child**_____

Signature of Parent/Guardian/ or Legally-authorized Representative_____ **Date**_____

STATEMENT OF PERSON WHO OBTAINED CONSENT

I have discussed the above points with the subject or, where appropriate, with the subject's legally authorized representative. It is my opinion that the subject understands the risks, benefits, and procedures involved with participation in this research study._____

(Signature of person who obtained consent)

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NATIONWIDE CHILDREN'S
When your child needs a hospital, everything matters.℠

CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY

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

PRINCIPAL INVESTIGATOR: Dr. Ruth Seabrook

CONTACT TELEPHONE NUMBER: 614-722-4650 (24 hours a day, 7 days a week) Ask unit clerk to page Dr. Ruth Seabrook or study team member.

STUDY SPONSOR: National Institutes of Health/NICHD Neonatal Research Network

SUBJECT'S NAME: _____ DATE OF BIRTH: _____

NOTE: The words "you" and "your" are used in this consent form. These words refer to the study volunteer whether a child or an adult.

1) INTRODUCTION

You and your baby are being invited to participate in a research study. Your baby's participation is voluntary, meaning you can choose whether or not you want your baby to participate. If you choose not to participate, there will be no loss of benefits to which your baby is otherwise entitled and your baby will continue to get the care that he/she needs.

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.

Participation is voluntary. Using this form as a guide, we will explain the study to you. If you have any questions about the study, please ask. Once you understand this study, we will ask you to decide whether you would like to participate or not. By signing this form, you agree to be in this study. If you do not want to be involved with this study, all regular and standard medical care will still be available to you. You also have the right to leave this study at any time, even if you agree to join now.

You will be given a signed and dated copy of the consent form.

2) WHY ARE WE DOING THIS RESEARCH STUDY?

Doctors and nurses need to better understand when we should transfuse blood (as red cells) into the blood of premature infants. Blood contains red cells, which carry a molecule called 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 how many red blood cells are circulating in your baby's body.

Because premature babies need intensive care, they need a lot of blood tests to monitor their care. Doctors try their best to order only a few blood tests depending on the needs of the premature babies. However since premature infants cannot make red blood cells easily, they sometimes become anemic, which means they have too few red blood cells. Therefore, we have to give them blood transfusions. We know that 90% of babies like yours receive at least one blood transfusion during their stay in the intensive care unit.

When the hemoglobin falls below a certain level, doctors will transfuse the baby. However, we know that some doctors tend to use a higher level of hemoglobin and some doctors tend to use a lower level of hemoglobin. The reason for this is that we do not know which level of hemoglobin is better.

This study has been designed to gather information to understand at which level of hemoglobin we should transfuse for the best results. The levels at which babies are being transfused in this study are well within the range at which doctors across the country routinely transfuse now. We are just trying to establish the best level, whether the best level is at the higher or lower end of the range.

This study has been approved and funded by the National Heart, Lung and Blood Institute and the Eunice Kennedy Shriver National Institute of Child Health and Human Development, branches of the National Institutes of Health and 18 large hospitals in the US are doing this study. Information about this study is available on a public registry website http://clinicaltrials.gov/ Identifier: NCT 01702805

3) WHERE WILL THE STUDY BE DONE AND HOW MANY SUBJECTS WILL TAKE PART?

This study will be done at several sites, including Nationwide Children's Hospital. Overall 1824 participants will take part in this study. We hope to enroll 300 participants here at Nationwide Children's Hospital.

4) WHAT WILL HAPPEN DURING THE STUDY AND HOW LONG WILL IT LAST?

If you agree to allow your baby to take part in this study, your baby will be randomly assigned (like the flip of a coin) to either the higher level of hemoglobin or the lower level. Both of these levels are in the usual range used by doctors in the NICU. The doctor will use this level of hemoglobin to decide when to transfuse your baby.

If your baby were to get unexpectedly ill, or have an unexpected urgent need for blood transfusion, your baby would get the transfusion regardless of the level of hemoglobin.

All of the blood tests done to check the hemoglobin level in the blood are done as routine standard of care. No additional blood draws will be required for research purposes.

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 22-26 month follow-up appointment will be conducted at the Nationwide Children's Hospital Neonatal Follow-up Clinic.

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. 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.

5) WHAT ARE THE RISKS OF BEING IN THIS STUDY?

We believe that there is very little chance that bad things will happen as a result of being in this study.

Your baby has been born very early, and is at risk for complications of extreme prematurity, and some of these babies die. There will be no extra blood tests done on your baby as a part of this study. All blood tests are done as routine standard of care at your doctor's request. This study does not alter the routine care for your baby. The risks associated with this study are exactly the same risks that exist in current medical practice and in blood transfusion therapy; however your baby may receive more blood transfusions while being in this study.

If your baby needs blood for emergency reasons, where all doctors would routinely give blood, they will get the blood they need – irrespective of the study. After that urgent need is over, they will then return to the study protocol.

Blood transfusions are, in general, extremely safe. It is simply that giving blood transfusions at too high a hemoglobin level may result not only in more blood transfusions, but the babies may take longer to mature their own bone marrow to produce their own blood. On the other hand, transfusing at too low hemoglobin could lead to the baby not having enough hemoglobin to carry enough oxygen around the body. We avoid these extremes by transfusing within the ranges of hemoglobin level that doctors already use.

During the entire study, an independent committee will review this study to make sure that it continues to be safe.

If you are worried about anything while in this study, please call the Principal Investigator or the study coordinator, Lina Yossef, at the telephone number listed on page 1.

6) ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

This study may not directly benefit your baby. However, your baby may benefit from additional monitoring during the study.

7) WHAT OTHER TREATMENTS OR OPTIONS ARE THERE?

If you choose not to participate in this study and if your baby needs a blood transfusion, the doctor will decide at which level of hemoglobin to use in make the decision to transfuse your baby.

8) WILL THERE BE ANY COSTS TO ME?

All costs related to the research parts of this study will be covered by the research team. However, the parts of the study that would be done for routine clinical care will be billed to you and to your insurance company or third party payer.

You will be paid $25 to cover the cost of travel at the time of the 22-26 month follow-up visit.

9) WHAT HAPPENS IF BEING IN THIS STUDY CAUSES INJURIES?

If you are hurt or get sick from something that was done as part of this study, doctors at the clinic or hospital can arrange for 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 have been injured from taking part in this study, call the study PI, Dr. Ruth Seabrook at (614) 722-3158 (Monday-Friday from 8am to 5pm). She 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 resulting from this study, you will not lose any legal rights by signing this form.

10) WHAT WILL HAPPEN IF NEW INFORMATION IS FOUND OUT ABOUT THE DRUG OR TREATMENT?

If new information is found out during this study that might change your mind about participating or might affect your health, a study staff member will discuss it with you as soon as possible.

11) WHAT HAPPENS IF I DO NOT FINISH THIS STUDY?

This study is expected to end after all participants have completed their 22 - 26 month neuro-developmental 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 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.

You have not followed study instructions.

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 any time. Withdrawal will not interfere with your future care.

12) OTHER IMPORTANT INFORMATION

Nationwide Children's Hospital is a teaching hospital and we are committed to doing research. Doing research will enable us to learn and provide the best care for our patients and families. You may be asked to participate in other research studies in the future. You have the right to decide to participate or decline to participate in any future studies. We will not share your contact information with researchers outside Nationwide Children's Hospital.

13) HOW WILL MY STUDY INFORMATION BE KEPT PRIVATE?

Information collected for this study may include information that can identify you. This is called "protected health information" or PHI. By agreeing to be in this study, you are giving permission to Dr. Ruth Seabrook and the study staff to collect, use, and disclose your PHI for this research study unless otherwise allowed by applicable laws. Information collected is the property of NICHD/Neonatal Research Network.

The reason why this PHI is collected, and what information will be used is listed below. The PHI will only be shared with the groups listed, but if you have a bad outcome or adverse event from being in this study, the Principal Investigator and staff or other health care providers may need to look at your entire medical records. In the event of any publication regarding this study, your identity will not be revealed.

The PHI collected or created under this research study will be used or disclosed as needed until the end of the study. The records of this study will be kept for an indefinite period of time and your authorization to use or disclose your PHI will not expire.

PHI that may be used or disclosed: Birth Date; Admission Date; Discharge Date; Date of Death; Name; Address; Telephone Number; Medical Record Number

People or Companies authorized to use, disclose, and receive PHI collected or created by this research study:

- PI and study staff
- The Nationwide Children's Hospital Institutional Review Board (the committee that reviews all human subject research)
- Nationwide Children's Hospital internal auditors
- The Office for Human Research Protections (OHRP) (the federal government office that oversees human subject research)
- Sponsor: NICHD/Neonatal Research Network
- Research Triangle International – NRN Data Coordinating Center
- Your insurance company (if charges are billed to insurance).

Because of the need to give information to these people, absolute confidentiality cannot be guaranteed. Information given to these people may no longer be protected by federal privacy rules.

Reason(s) why the use or disclosure is being made: To locate medical charts, to contact you in the future, for future tracking, or in the event of a bad outcome or adverse reaction.

You may decide not to authorize the use and disclosure of your PHI. However, if it is needed for this study, you will not be able to be in this study. If you agree to be in this study and later decide to withdraw your participation, you may withdraw your authorization to use your PHI. This request must be made in writing to the Principal Investigator, Dr. Ruth Seabrook at Nationwide Children's Hospital, Division of Neonatology, 700 Children's Drive, Columbus, Ohio 43205. If you withdraw your authorization, no new PHI may be collected and the PHI already collected may not be used unless it has already been used or is needed to complete the study analysis and reports.

14) WHOM SHOULD I CALL IF I HAVE QUESTIONS OR PROBLEMS?

If you have questions, concerns, or complaints about anything while on this study or you have been injured by the research, you have 24 hour access to talk to the Principal Investigator at 614-722-4650 Ask unit clerk to page Dr. Ruth Seabrook or study coordinator, Lina Yossef.

If you have questions, concerns, or complaints about the research; if you have questions about your rights as a research volunteer; if you cannot reach the Principal Investigator; or if you want to call someone else - please call (614) 722-2708, Nationwide Children's Hospital Institutional Review Board, (IRB, the committee that reviews all research involving human subjects at Nationwide Children's Hospital).

Subject's Name _____ **Date of Birth**_____

SUBJECT or SUBJECT'S PARENT OR PERSON AUTHORIZED TO CONSENT ON BEHALF OF THE CHILD (SUBJECT TO THE SUBJECT'S GENERAL MEDICAL CARE)

I have read this consent form and I have had an opportunity to ask questions about this research study. These questions have been answered to my satisfaction. If I have more questions about participating in this study or a research-related injury, I may contact the Principal Investigator. By signing this consent form, I certify that all health information I have given is true and correct to the best of my knowledge.

I have been given a copy of the Nationwide Children's Hospital Notice of Privacy Practices. If allowed by law, I understand that my right to any information that is created or collected by Nationwide Children's Hospital for this study can be temporarily suspended if necessary for the purposes of this research project. I also understand that my right to access to this information from this study will be reinstated upon completion of this research unless I have been told by the Principal Investigator that I will not receive study results.

I agree to participate in this study or I give permission for my child to participate in this study. I will be given a copy of this consent form with all the signatures for my own records.

CONSENT SIGNATURES

_____ _____
SUBJECT or SUBJECT'S LEGAL REPRESENTATIVE **DATE & TIME AM/PM**

_____ _____
SUBJECT or SUBJECT'S LEGAL REPRESENTATIVE **DATE & TIME AM/PM**

Permission of the second parent not obtained because (select all that apply):
_____ Not required by the IRB (risk level 1 or 2).
_____ Other parent is deceased.
_____ Other parent is unknown.
_____ Other parent is not reasonably available.
_____ Only one parent has legal responsibility for the care and custody of subject.

_____ _____
PERSON OBTAINING CONSENT **DATE & TIME AM/PM**

I certify that I have explained the research, its purposes,
And the procedures to the subject or the subject's legal
Representatives before requesting their signatures.

The University of New Mexico Health Sciences Center
Consent to Participate in Research

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?

January 9, 2013

Purpose and General Information

You are being asked to participate in a research study that is being done by Dr. Robin Ohls, who is the Principal Investigator, and her associates from the Department of Pediatrics/Neonatology. This research is being done to better understand when we should transfuse red blood cells into premature infants. You are being asked to participate because your baby was born prematurely (before 29 weeks gestation) and is extremely small (less than 2 pounds 4 ounces). Approximately 30 babies will take part in this study at the University of New Mexico newborn intensive care unit (NICU) and a total of 1824 babies will participate nationwide.

Because premature babies need intensive care, they need a lot of blood tests to monitor their care. Doctors try their best to order only a few blood tests depending on the needs of the premature babies. Since premature babies cannot make red blood cells easily, their amount of red cells decreases and need to be replaced by a blood transfusion. When the number of red cells (called the hematocrit) falls below a certain level, doctors will transfuse the baby. However, we know that some doctors transfuse babies at a higher hematocrit and some doctors transfuse at a lower hematocrit. We do not know which level of hematocrit is better. This study will help answer that question.

This study has been designed to determine what level of hematocrit we should transfuse for the best results. This study has been approved and funded by the National Heart, Lung and Blood Institute and the Eunice Kennedy Shriver National Institute of Child Health and Human Development, branches of the National Institutes of Health and 18 large hospitals in the US are doing this study. Information about this study is available on a public registry website (http://clinicaltrials.gov/ Identifier: NCT 01702805)

This form will explain the study to you, including the possible risks as well as the possible benefits of participating, so you can make an informed choice about whether or not to allow your baby to participate in this study. Please read this Consent Form carefully. Ask the investigators or study staff to explain any words or information that you do not clearly understand.

What will happen if I allow my baby to participate?

If you agree for your baby to be in this study, you will be asked to read and sign this Consent Form. After you sign the Consent Form, the following things will happen: Your baby will be randomly assigned (like a

flip of a coin) to either the higher level of hematocrit or the lower level. Both of these levels are in the usual range used by doctors in the NICU. The doctor will use this level of hematocrit to decide when to transfuse the baby. If your baby needs blood for emergency reasons, they will get the blood they need regardless of what level they are assigned to. After that urgent need is over, they will then return to the study protocol.

There are no blood tests required for the study. We will ask you to complete an economic questionnaire that will provide us with information on how families cope with having a baby in the NICU.

We will arrange for your baby to come back when they 2 years old are for a follow-up appointment. All extremely premature babies are routinely seen at around 2 years of age to check how well they are growing and developing. We will observe how well your baby 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 NICU.

What are the possible risks or discomforts of being in this study?
Your baby has been born very early, and is at risk for complications of extreme prematurity. Some babies born very prematurely do not survive. This study does not carry any additional risks to your baby if you choose to take part. There are no extra blood tests being done on your baby. The risks associated with this study are exactly the same risks that exist in current medical practice and in blood transfusion therapy.

While blood transfusions are considered extremely safe, there is a very small risk of infection or transfusion reaction. The risk of being in the lower hematocrit group is no greater than the general population in the NICU, as our standard hematocrit levels are the same or slightly lower than the lower hematocrit group. During the entire study, an independent committee will review this study to make sure that it continues to be safe.

The risk of randomization is that treatment outcome may be better for babies in one arm of the study or the other. Babies in the less effective arm may not do as well as babies in the more effective arm.

Every effort will be made to protect the information you give us. However, there is a small risk of loss of privacy and/or confidentiality. There may also be a risk of stress or emotional distress.

How will my child's information be kept confidential?
Your baby's name and other identifying information will be maintained in locked files, available only to authorized members of the research team, for the duration of the study. For any information entered into a computer, the only identifier will be a unique study identification (ID) number. Any personal identifying information and any record linking that information to study ID numbers will be destroyed when the study is completed. Information resulting from this study will be used for research purposes and may be published; however, your baby will not be identified by name in any publications.

Information from your participation in this study may be reviewed by the sponsor, federal and state regulatory agencies, and by the UNM Human Research Review Committee (HRRC) which provides regulatory and ethical oversight of human research. There may be times when we are required by law to share your baby's information. However, your baby's name will not be used in any published reports about this study.

What are the benefits to being in this study?
There may or may not be direct benefit to you or your baby from being in this study. However, your baby's participation may help find out the strategy for red blood cell transfusions in very premature babies which gives the best outcome.

What other choices do we have if my child doesn't participate?
Taking part in this study is voluntary so you can choose not to participate.

Will I be paid for taking part in this study?
You will not receive any payments for your baby taking part in this study. However, if necessary, we will cover the cost of travel for your baby's visit at around 2 years of age.

What will happen if I am injured or become sick because I took part in this study?
If your child is injured or become sick as a result of this study, UNMHSC will provide emergency treatment.

No commitment is made by the University of New Mexico Health Sciences Center (UNMHSC) to provide free medical care or money for injuries to participants in this study.

In the event that your baby has an injury or illness that is caused by their participation in this study, reimbursement for all related costs of care will be sought from your insurer, managed care plan, or other benefits program. If you do not have insurance, you may be responsible for these costs. You will also be responsible for any associated co-payments or deductibles required by your insurance.

It is important for you to tell the investigator immediately if your baby has been injured or becomes sick because of taking part in this study. If you have any questions about these issues, or believe that you or your baby have been treated carelessly in the study, please contact the Human Research Review Committee (HRRC) at the (505) 272-1129 for more information.

How will I know if you learn something new that may change my mind about participating?
You will be informed of any significant new findings that become available during the course of the study, such as changes in the risks or benefits resulting from participating in the research or new alternatives to participation that might change your mind about your baby participating.

Can I stop being in the study once I begin?

Yes. You can withdraw your baby from this study at any time without affecting your baby's access to care. The investigators have the right to end your baby's participation in this study if they determine that he/she no longer qualifies to take part or if it is in their best interest or the study's best interest to stop your baby's participation. The Sponsor may stop the study at any time.

HIPAA Authorization for Use and Disclosure of Your Protected Health Information (HIPAA)

As part of this study, we will be collecting health information about your baby and sharing it with others. This information is "protected" because it is identifiable or "linked" to you and your baby.

Protected Health Information (PHI)

By signing this Consent Document, you are allowing the investigators and other authorized personnel to use your baby's protected health information for the purposes of this study. This information may include: supporting information from your baby's entire medical record, results of lab tests and information from follow-up visits.

In addition to researchers and staff at UNMHSC and other groups listed in this form, there is a chance that your baby's health information may be shared (re-disclosed) outside of the research study and no longer be protected by federal privacy laws. Examples of this include disclosures for law enforcement, judicial proceeding, health oversight activities and public health measures.

Right to Withdraw Your Authorization

Your authorization for the use and disclosure of your baby's health information for this study shall not expire unless you cancel this authorization. Your baby's health information will be used or disclosed as long as it is needed for this study. However, you may withdraw your authorization at any time provided you notify the UNM investigators in writing. To do this, please send a letter notifying them of your withdrawal to:

Robin Ohls, M.D
MSC 10 5590
1 University of New Mexico
Albuquerque New Mexico 87131

Please be aware that the research team will not be required to destroy or retrieve any of your baby's health information that has already been used or shared before your withdrawal is received.

Refusal to Sign

If you choose not to sign this consent form and authorization for the use and disclosure of your baby's PHI, you will not be allowed to take part in the research study.

What if I have questions or complaints about this study?

If you have any questions, concerns or complaints at any time about the research study, Robin Ohls, M.D., or her associates will be glad to answer them at (505) 272-6410, Monday through Friday 8:00 am – 5:00 pm. If you need to contact someone after business hours or on weekends, please call the University of New Mexico Hospital operator at (505) 272-2111 and ask for the faculty physician on call for Neonatology. If you would like to speak with someone other than the research team, you may call the Human Research Review Committee (HRRC) at (505) 272-1129. The HRRC is a group of people from UNMHSC and the community who provide independent oversight of safety and ethical issues related to research involving human participants.

What are my baby's rights as a research participant?
If you have questions regarding your baby's rights as a research participant, you may call the Human Research Protections Office (HRPO) at (505) 272-1129 or visit the HRPO website at http://hsc.unm.edu/som/research/hrrc/.

Consent and Authorization
You are making a decision whether to have your baby participate in this study. Your signature below indicates that you read the information provided (or the information was read to you). By signing this Consent Form, you are not waiving any of your legal rights as a research participant.

I have had an opportunity to ask questions and all questions have been answered to my satisfaction. By signing this Consent Form, I agree to let my baby participate in this study and give permission for my and my baby's health information to be used or disclosed as described in this Consent Form. A copy of this Consent Form will be provided to me and one will be placed in my child's medical record.

_____
Name of Subject (print)

_____ _____/_____
Name of Parent/Legal Guardian (print) Signature of Adult Participant Date

I have explained the research to the participant and answered all of his/her questions. I believe that he/she understands the information in this consent form and freely consents to participate.

_____ _____/_____
Name of Research Team Member Signature of Research Team Member Date

University of Pennsylvania
Office of Regulatory Affairs
3624 Market St., Suite 301 S
Philadelphia, PA 19104-6006
Ph: 215-573-2540/ Fax: 215-573-9438
INSTITUTIONAL REVIEW BOARD
(Federalwide Assurance # 00004028)

28-Feb-2013

Haresh M Kirpalani
kirpalanih@email.chop.edu

PRINCIPAL INVESTIGATOR	: Haresh M Kirpalani
TITLE	: 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?
SPONSORING AGENCY	: National Heart, Lung, and Blood Institute/NIH/DHHS
PROTOCOL #	: 816868
REVIEW BOARD	: IRB #1

Dear Dr. Haresh Kirpalani:

The documents noted below, for the above-referenced protocol, were reviewed by Dr. Emma Meagher, Executive Chair of the IRB (or her authorized designee) using the expedited procedure set forth in 45 CFR 46.110 and approved on 27-Feb-2013.

-HS ERA Modification, confirmation code: bbgihgeb, submitted 2.25.13
-Cover Letter, dated 2.21.13
-Cover Letter re: response to preliminary review, dated 2.25.13
-Revised Informed Consent & HIPAA Authorization Form, version 5, uploaded 2.25.13

If you have any questions about the information in this letter, please contact the IRB administrative staff. Contact information is available at our website: http://www.upenn.edu/regulatoryaffairs.

Thank you for your cooperation.

Sincerely,

IRB Administrator

Penn Medicine

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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
Short Title:	Transfusion of Prematures (TOP)
Principal Investigators:	Haresh Kirpalani, BM, MSc (CHOP) 215-300-9475 Barbara Schmidt, MD (HUP) 215-662-3228 Soraya Abbasi, MD (PAH) 215-829-3301
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 Nursey; (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 – 28 6/7 weeks gestational age with a birth weight of less than or equal to 1000 gram are eligible for this study. Babies like yours, who are born extremely premature and who need intensive care, require a lot of clinically required blood tests ordered by the doctors looking after your baby. This study does not ask for any extra blood tests. However blood tests remove baby's own red cells which contain hemoglobin. Babies cannot easily form new blood cells from their bone marrow because it is premature. Very premature babies frequently become anemic (or have a low hemoglobin) and often require blood transfusion. We know that 90% of babies like yours receive at least one blood transfusion during their stay in the intensive care unit.

This study is trying to provide an answer to the question: "What is the best level of hemoglobin for transfusing babies?", by better understanding when it is best to transfuse blood (as red cells) into the blood of premature infants. Hemoglobin, carries oxygen and is used to measure how many red blood cells your baby has. Hemoglobin is essential for life as it carries oxygen around the body. Hemoglobin is used by doctors as a measure of how many red blood cells are circulating in your baby's body.

We know that some doctors tend to use the higher levels of hemoglobin and some doctors tend to use the lower levels. This is because at the moment, no one knows which level of hemoglobin is better.

The levels at which babies are being transfused in this study are well within the 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, a branch of the National Institutes of Health and 18 large hospitals in the US are doing this study.

You can see this on a public website (http://clinicaltrials.gov) using the identifier: NCT01702805.

How long will my baby be 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 trigger 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 Folllow-up clinic.

What does the study involve?

If you agree that your baby should take part in this study, your baby will be randomly assigned (like a flip of a coin to say 'heads' or 'tails') to be given blood transfusions according to either higher level(s) of hemoglobin or lower level(s). The doctor will use this level of hemoglobin to decide when to transfuse the baby. Normally, the doctor's decision to transfuse is also based on the day of life of the infant and the respiratory status at the time.

How the decision to transfuse is determined ?

The decision to transfuse is very similar to normal clinical decisions and is based on respiratory support as needed and the baby's age.

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 the 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.

In Addition We ask for you to complete a questionnaire

We will ask you to complete an 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. 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 collect information from the hospital 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.

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** does include the risk associated with an IV placement if your baby does not already have an IV at the time that your baby needs a blood transfusion. There are no extra blood tests being done on your baby for this study. The risks associated with this study are exactly the same risks that exist in current medical practice and in blood transfusion therapy.

Blood transfusions are relatively safe, nowadays. It is simply that giving blood transfusions at too high a hemoglobin level may result not only in more blood transfusions, but the babies may take longer to mature their own bone marrow to produce their own blood. On the other hand, transfusing at too low a hemoglobin level, could lead to the baby not having enough hemoglobin to carry enough oxygen around the body. We avoid these extremes by transfusing within the ranges that are considered appropriate by experts in the field.

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.

What other choices do I have if I do not participate?

If you choose not to participate in this study and if your baby needs a blood transfusion, the doctor will decide at which level of hemoglobin to use in making the decision to transfuse your baby. The alternative to enrolling your child in this study is not to participate, as these interventions are available to you outside of the research study.

Will I be paid for being in this study?

You will not receive any payments for taking part in this study. However, if necessary, we will cover the cost of travel to the CHOP follow up clinic for the visit at 22 to 26 months, if for some reason you are unable to attend.

Will I have to pay for anything?

While you are in this study, the cost of your 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 you are hurt or get sick from something that was done as part of this study, doctors at the clinic or hospital can arrange for 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 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 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 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.
- You have not followed study instructions.
- 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 future care.

Who can see or use my information? How will my personal information be protected?

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.

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 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 rights as a research subject?

If you have questions, concerns or complaints regarding your participation in this research study or if you have any questions about your 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.

Parental Informed Consent Form

When you sign this form, you are agreeing 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 volunteer. Your signature also means that you are permitting the University of Pennsylvania to use your 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.

A copy of this consent form will be given to you.

_____
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 subject Representative **[print]**	Authorized subject representative Signature	Date

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

_____

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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
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Principal Investigators:	Haresh Kirpalani, BM, MSc (CHOP) 215-300-9475 Barbara Schmidt, MD (HUP) 215-662-3228 Soraya Abbasi, MD (PAH) 215-829-3301
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 Nursey; (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.

What is the purpose of this research study?

Babies who are born between 22 – 28 6/7 weeks gestational age with a birth weight of less than or equal to 1000 gram are eligible for this study. Your baby meets these criteria. Babies like yours, who are born extremely premature and who need intensive care, require a lot of blood tests. Because they cannot form new blood cells as fast as they are being removed, very premature babies become anemic and often require blood transfusion. We know that 90% of babies like yours receive at least one blood transfusion during their stay in the intensive care unit.

This study is trying to provide an answer to the question: "What is the best level of hemoglobin for transfusing babies?". Medical teams looking after small babies need to better understand when it is best to transfuse blood (as red cells) into the blood of premature infants. Blood contains red cells, which carry a molecule called hemoglobin. Hemoglobin is essential for life as it carries oxygen around the body. Hemoglobin is used by doctors as a measure of how many red blood cells are circulating in your baby's body.

Because premature babies need intensive care, they need a lot of blood tests to monitor their care, and medical teams try their best to order only the blood tests really needed. However since premature infants cannot make red blood cells easily, they often become anemic. Therefore, your baby would get blood transfusions.

Normally anemia is defined by the level of hemoglobin in the blood and blood transfusions are given when hemoglobin falls below a certain level. It is routine to receive blood transfusions at hemoglobin levels based on your doctor's choice. However in preterms, no one knows where this level actually is. We have found that some doctors tend to use the higher levels and some doctors tend to use the lower levels. This is because at the moment, no one knows which level of hemoglobin is better.

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

These blood transfusions are given when the hemoglobin falls below a certain level. However, there are some advantages to keeping the hemoglobin high and some advantages to keeping the hemoglobin low. Therefore, some doctors prefer to use a higher level of hemoglobin and some doctors prefer to use a lower level of hemoglobin. We do not know which level of hemoglobin is better. This study aims to help us find out when we should best transfuse babies.

This study has been designed to help neonatal caregivers understand at which level of hemoglobin should be transfused for improved outcomes. This study has been approved and funded by the National Heart, Blood and Lung Institute, a branch of the National Institutes of Health and 18 large hospitals in the US are doing this study.

Information about this study is available on a public registry website (http://clinicaltrials.gov). In order to search for this trial on the website, please enter the identifier: NCT01702805.

How long will my baby be in the study? How many other babies will be 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 trigger will only apply to the ICN admission. The 22-26 month follow-up appointment will be conducted at any of the 3 CHOP affiliated Neonatal Follow-up clinics. If you are unable to come to any of the CHOP affiliated Neonatal Follow-up clinics, we will help you to find an alternative Folllow-up clinic.

This study will enroll 1824 babies from across the country in 18 sites of the National Institute of Child Health and Human Development (NICHD) Network.

What does the study involve?

If you agree that your baby should take part in this study, your baby will be randomly assigned (like a flip of a coin to say 'heads' or 'tails') to be given blood transfusions according to either higher level(s) of hemoglobin or lower level(s). Both of these levels are in the usual range used by doctors in the NICU. The doctor will use this level of hemoglobin to decide when to transfuse the baby. Normally, the doctor's decision to transfuse is also based on the day of life of the infant and the respiratory status at the time. Therefore, in this study, the transfusions are determined in the following sequence.

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

(1) Determine respiratory status of the infant. Does the infant require respiratory support or no support? Depending upon the response, adhere to the respective column.

(2) Determine the postnatal age of the infant:
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 depending upon the randomization group that your baby has been assigned.

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 the transfusion. Babies can receive blood transfusions outside of their randomization arm if there is an unexpected urgent need for a blood transfusion. Once the baby has stabilized, future blood transfusion needs will be determined by the randomization arm.

Your baby will not receive any extra blood tests because of this study. All of the blood tests that are done are routine standard of care.

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

We will collect information from the hospital 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.

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. You are free to decline to answer some or all of these questions on the questionnaire.

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** does include the risk associated with an IV placement if your baby does not already have an IV at the time that your baby needs a blood transfusion. There are no extra blood tests being done on your baby. All blood tests are done as routine standard of care at your doctor's request. The risks associated with this study are exactly the same risks that exist in current medical practice and in blood transfusion therapy.

As routine standard of care, you will be asked to sign a hospital-based consent form to allow your baby to receive blood transfusions as part of your baby's care in the hospital. This hospital-based consent form has nothing to do with this study. The hospital-based consent form mentions the general risks associated with the transfusion of blood that include allergic reaction, fever, hemolytic transfusion reactions (when transfused red blood cells are destroyed by antibodies in the circulation), transfusion related lung injury (TRALI) and transmission of infectious diseases such as hepatitis and AIDS. Although the risks of transmission of infectious diseases exist, they are nowadays very rare because of very by careful testing of the blood in compliance with federal law.

If your baby needs blood for emergency reasons, where all doctors would routinely give blood, they will get the blood they need – irrespective of the study. After that urgent need is over, they will then return to the study protocol.

Blood transfusions are relatively safe, nowadays. It is simply that giving blood transfusions at too high a hemoglobin level may result not only in more blood transfusions, but the babies may take longer to mature their own bone marrow to produce their own blood. On the other hand, transfusing at too low a hemoglobin level, could lead to the baby not having enough hemoglobin to carry enough oxygen around the body. We avoid these extremes by transfusing within the ranges that are considered appropriate by experts in the field.

The reason that doctors vary so much regarding which hemoglobin to transfuse at, is that transfusing at both high and low levels have pluses and minuses. For transfusing at a high level, it is possible that better oxygen levels leads to a better organ function; but it is also possible that this gives higher iron levels (which may lead to tissue damage), and a higher infection rate.

On the other hand, for transfusing at a lower hemoglobin transfusion level, this leads to fewer transfusions - the higher iron levels and infections possibly related to transfusions are avoided. But this is accompanied by potentially lower oxygen levels which may adversely affect organ function.

This "trade off" between competing risks and benefits of blood transfusions, is why doctors are still uncertain about when to transfuse." During the entire study, an independent monitoring committee will review this study to make sure that it continues to be safe. This committee of experts is drawn from the NIH.

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.

What other choices do I have if I do not participate?

If you choose not to participate in this study and if your baby needs a blood transfusion, the doctor will decide at which level of hemoglobin to use in making the decision to transfuse your baby. The alternative to enrolling your child in this study is not to participate, as these interventions are available to you outside of the research study.

Will I be paid for being in this study?

You will not receive any payments for taking part in this study. However, if necessary, we will cover the cost of travel to the CHOP follow up clinic for the visit at 22 to 26 months, if for some reason you are unable to attend.

Will I have to pay for anything?

While you are in this study, the cost of your 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 you are hurt or get sick from something that was done as part of this study, doctors at the clinic or hospital can arrange for 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 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 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 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.
- You have not followed study instructions.
- 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 future care.

Who can see or use my information? How will my personal information be protected?

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. Please refer to the "HIPAA Privacy Authorization" section of this document (included below) that explains more specifically how you and your baby's personal information will be protected.

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.

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 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 rights as a research subject?

If you have questions, concerns or complaints regarding your participation in this research study or if you have any questions about your 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.

Authorization for Use and Disclosure of Health Information

How will my and my baby's personal information be protected?

What information about me and my baby may be collected, used or shared with others?

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

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

Why are my and my baby's information being used?

- To do the research
- To oversee the research
- To see if the research was done right.

We need to collect health information about you and your baby in order to conduct this study. This will include information from medical records and the results of the follow-up exam at 22 -26 months. We will do our best to keep your and your baby's personal information private and confidential. However, we cannot guarantee absolute confidentiality. Your and your baby's personal information may be disclosed if required by law.

The results of this study may be shown at meetings or published in journals to inform other doctors and health professionals. We will keep your and your baby's identity private in any publication or presentation about the study.

Who may use and share information about me or my baby?

The following individuals may use or share your and your baby's information for this research study:

• The Principal Investigator and the Investigator's study team
• Authorized members of the workforce of the UPHS and the School of Medicine, and University of Pennsylvania support offices, who may need to access you and your information in the performance of their duties (for example: for research oversight and monitoring, to provide treatment, to manage accounting or billing matters, etc.).

Who, outside of the School of Medicine, might receive my and my baby's information?

Individuals or organizations responsible for administering the study:
- Members of the clinical team and research team at the Hospital of the University of Pennsylvania, Pennsylvania Hospital and the Children's Hospital of Philadelphia
- Your baby's personal health information from this clinical trial may be disclosed to your referring institution in order to better manage your baby's
- The National Institutes of Health Neonatal Research Network
- National Heart, Lung and Blood Institute
- Data Safety Monitoring Committee (DSMC)
- Research Triangle Institute (the organization that will analyze the data)
- The Food and Drug Administration
- The Office of Human Research Protections

Your baby's name will not be used in any published reports about this study. A copy of this consent form will be placed in your baby's medical record. Information contained in your baby's study records is identified with a code rather than your baby's name. This coded information will be shared with the sponsor of the study by a computer. The list which links your baby's name to the code will be kept in the locked office of Neonatology at Pennsylvania Hospital, The Hospital University of Pennsylvania or The Children's Hospital of Philadelphia.

Once you or your baby's personal health information is disclosed to others outside 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 the School of Medicine use or disclose my or my baby's personal health information?

Your authorization for use of your and your baby's personal health information for this specific study does not expire.

Your and your baby's information may be held in a research database. However, 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
• The University of Pennsylvania's Institutional Review Board grants permission
• As permitted by law

Can I change my mind about giving permission for use of my or my baby's information?

Yes. You may withdraw your permission to use and disclose your and your baby's health information at any time. You do this by sending written notice to the study investigator. If you withdraw your permission, your baby will not be able to stay in this study.

What if I decide not to give permission to use and give out my and my baby's health information?

Then your baby will not be able to be in this research study.
By signing this document you are permitting the School of Medicine to use and disclose personal health information collected about you and your baby for research purposes as described above.

Parental Informed Consent and HIPAA Authorization Form

When you sign this form, you are agreeing 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 volunteer. Your signature also means that you are permitting the University of Pennsylvania to use your 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.

A copy of this consent form will be given to you.

_____
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 subject Representative **[print]**	Authorized subject representative Signature	Date

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

_____

Penn Medicine

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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
Short Title:	Transfusion of Prematures (TOP)
Principal Investigators:	Haresh Kirpalani, BM, MSc (CHOP) 215-300-9475 Barbara Schmidt, MD (HUP) 215-662-3228 Soraya Abbasi, MD (PAH) 215-829-3301
Emergency Contact:	Neonatology Attending on-call for HUP/CHOP (215) 300-9475 PAH Intensive Care Nursery: 215-829-5070

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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.

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This study is trying to provide an answer to the question: "What is the best level of hemoglobin for transfusing babies?". Medical teams looking after small babies need to better understand when it is best to transfuse blood (as red cells) into the blood of premature infants. Blood contains red cells, which carry a molecule called hemoglobin. Hemoglobin is essential for life as it carries oxygen around the body. Hemoglobin is used by doctors as a measure of how many red blood cells are circulating in your baby's body.

Because premature babies need intensive care, they need a lot of blood tests to monitor their care, and medical teams try their best to order only the blood tests really needed. However since premature infants cannot make red blood cells easily, they often become anemic. Therefore, your baby would get blood transfusions.

Normally anemia is defined by the level of hemoglobin in the blood and blood transfusions are given when hemoglobin falls below a certain level. It is routine to receive blood transfusions at hemoglobin levels based on your doctor's choice. However in preterms, no one knows where this level actually is. We have found that some doctors tend to use the higher levels and some doctors tend to use the lower levels. This is because at the moment, no one knows which level of hemoglobin is better.

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

These blood transfusions are given when the hemoglobin falls below a certain level. However, there are some advantages to keeping the hemoglobin high and some advantages to keeping the hemoglobin low. Therefore, some doctors prefer to use a higher level of hemoglobin and some doctors prefer to use a lower level of hemoglobin. We do not know which level of hemoglobin is better. This study aims to help us find out when we should best transfuse babies.

This study has been designed to help neonatal caregivers understand at which level of hemoglobin should be transfused for improved outcomes. This study has been approved and funded by the National Heart, Blood and Lung Institute, a branch of the National Institutes of Health and 18 large hospitals in the US are doing this study.

Information about this study is available on a public registry website (http://clinicaltrials.gov). In order to search for this trial on the website, please enter the identifier: NCT01702805.

How long will my baby be in the study? How many other babies will be 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 trigger will only apply to the ICN admission. The 22-26 month follow-up appointment will be conducted at any of the 3 CHOP affiliated Neonatal Follow-up clinics. If you are unable to come to any of the CHOP affiliated Neonatal Follow-up clinics, we will help you to find an alternative Folllow-up clinic.

This study will enroll 1824 babies from across the country in 18 sites of the National Institute of Child Health and Human Development (NICHD) Network.

What does the study involve?

f you agree that your baby should take part in this study, your baby will be randomly assigned (like a flip of a coin to say 'heads' or 'tails') to be given blood transfusions according to either higher level(s) of hemoglobin or lower level(s). Both of these levels are in the usual range used by doctors in the NICU. The doctor will use this level of hemoglobin to decide when to transfuse the baby. Normally, the doctor's decision to transfuse is also based on the day of life of the infant and the respiratory status at the time. Therefore, in this study, the transfusions are determined in the following sequence.

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

(1) Determine respiratory status of the infant. Does the infant require respiratory support or no support? Depending upon the response, adhere to the respective column.

(2) Determine the postnatal age of the infant:

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 depending upon the randomization group that your baby has been assigned.

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 the transfusion. Babies can receive blood transfusions outside of their randomization arm if there is an unexpected urgent need for a blood transfusion. Once the baby has stabilized, future blood transfusion needs will be determined by the randomization arm.

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information or your social security number. This will help us determine the cost of taking care of premature babies today in the United States.

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. You are free to decline to answer some or all of these questions on the questionnaire.

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** does include the risk associated with an IV placement if your baby does not already have an IV at the time that your baby needs a blood transfusion. There are no extra blood tests being done on your baby. All blood tests are done as routine standard of care at your doctor's request. The risks associated with this study are exactly the same risks that exist in current medical practice and in blood transfusion therapy.

As routine standard of care, you will be asked to sign a hospital-based consent form to allow your baby to receive blood transfusions as part of your baby's care in the hospital. This hospital-based consent form has nothing to do with this study. The hospital-based consent form mentions the general risks associated with the transfusion of blood that include allergic reaction, fever, hemolytic transfusion reactions (when transfused red blood cells are destroyed by antibodies in the circulation), transfusion related lung injury (TRALI) and transmission of infectious diseases such as hepatitis and AIDS. Although the risks of transmission of infectious diseases exist, they are nowadays very rare because of very by careful testing of the blood in compliance with federal law.

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Blood transfusions are relatively safe, nowadays. It is simply that giving blood transfusions at too high a hemoglobin level may result not only in more blood transfusions, but the babies may take longer to mature their own bone marrow to produce their own blood. On the other hand, transfusing at too low a hemoglobin level, could lead to the baby not having enough hemoglobin to carry enough oxygen around the body. We avoid these extremes by transfusing within the ranges that are considered appropriate by experts in the field.

The reason that doctors vary so much regarding which hemoglobin to transfuse at, is that transfusing at both high and low levels have pluses and minuses. For transfusing at a high level, it is possible that better oxygen levels leads to a better organ function; but it is also possible that this gives higher iron levels (which may lead to tissue damage), and a higher infection rate.
On the other hand, for transfusing at a lower hemoglobin transfusion level, this leads to fewer transfusions - the higher iron levels and infections possibly related to transfusions are avoided. But this is accompanied by potentially lower oxygen levels which may adversely affect organ function.

This “trade off” between competing risks and benefits of blood transfusions, is why doctors are still uncertain about when to transfuse.”

During the entire study, an independent monitoring committee will review this study to make sure that it continues to be safe. This committee of experts is drawn from the NIH.

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This study may not directly benefit your baby.

What other choices do I have if I do not participate?

If you choose not to participate in this study and if your baby needs a blood transfusion, the doctor will decide at which level of hemoglobin to use in making the decision to transfuse your baby. The alternative to enrolling your child in this

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

If you think you 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.

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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 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.
- You have not followed study instructions.
- 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 future care.

Who can see or use my information? How will my personal information be protected?

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.

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 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 rights as a research subject?

If you have questions, concerns or complaints regarding your participation in this research study or if you have any questions about your 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.

Parental Informed Consent Form

When you sign this form, you are agreeing 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 volunteer. Your signature also means that you are permitting the University of Pennsylvania to use your 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.

A copy of this consent form will be given to you.

_____
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 subject Representative **[print]**	Authorized subject representative Signature	Date

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

_____

University at Buffalo
Children & Youth Institutional Review Board (CYIRB)
Women & Children's Hospital of Buffalo
219 Bryant Street – Buffalo, NY 14222

Parental Permission to Participate in a Research Study

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?

Short Title: Transfusion of Prematures (TOP)

It is a principle of medical ethics that the subjects of a research project be informed about the research before giving their consent to participate.

You are being asked to give permission for your child to participate in a research study. The purpose of this document is to provide you with information so you can decide whether to give permission for your child to participate in this research study. Your permission should be given based on your understanding of the purpose and benefits of the treatment, device, or procedures that are being used, any potential risks of participation, and whether treatment or compensation is available for physical injuries that result from research procedures. Your decision to give permission for your child to participate in this research is voluntary. If you choose not to give permission for your child to participate in this study or choose to withdraw him/her from the research project at any time, it will have no effect on the quality of his/her future medical care. Please ask questions if there is anything that you do not understand. You have the right to ask for additional information at any time.

1. INVESTIGATOR(S) CONDUCTING THE STUDY

Who is conducting the study?

Dr. Satyan Lakshminrusimha
Dr. Anne Marie Reynolds
Dr. Vivien Carrion
Dr. Corinne Leach
Dr. Vasanth Kumar
Dr. Bobby Mathew
Dr. Sfurti Nath
Dr. Jayasree Nair
Dr. Devaraj Sambalingam
Dr. Vinay Sharma
Dr. Valerie Elberson

Site Principal Investigator:
Satyan Lakshminrusimha, MD
Division of Neonatology
Women and Children's Hospital of Buffalo
219 Bryant Street
Buffalo, NY 14222
Phone: 716-878-7673

Principal Investigator:
Haresh Kirpalani, BM, MSc
Division of Neonatology and Newborn Services
Hospital of the University of Philadelphia
34th and Spruce Street
Philadelphia, PA 19104
Phone: 215-662-3228

Study Consent Version Date: April 25, 2013

Parent's Initials: _____

2. SOURCE OF SUPPORT

Who is sponsoring the research project?

Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), a branch of the National Institute of Health

3. SITES OF THE RESEARCH STUDY

Where will the study take place?

University at Buffalo/University of Rochester, NY
Case Western Reserve University, Cleveland, OH
University of Texas-Dallas, TX
Wayne State University, Detroit, MI
Emory University, Atlanta, GA
University of Cincinnati, Cincinnati, OH
Indiana University, Indianapolis, IN
Brown University, Providence, RI
Stanford University, Palo Alto, CA
University of Alabama, Birmingham, AL
University of Texas -Houston, TX
Duke University, Durham, NC
University of Iowa, Iowa City, IA
University of New Mexico, NM
University of Pennsylvania, PA
University of California at Los Angeles, CA
Nationwide Children's Hospital, Columbus, OH
Children's Mercy Hospital, Kansas City, MO

4. PURPOSE OF THE RESEARCH STUDY

What is the purpose of the research study?

Doctors and nurses need a better understanding of when we should transfuse blood (as red blood cells) into the blood of premature infants. We know that 90% of babies like yours receive at least one blood transfusion during their stay in the intensive care unit. Blood contains red blood cells, which carry a molecule called 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 how many red blood cells are circulating in your baby's body. Because premature babies need intensive care, they require a lot of blood tests to monitor their care. Doctors try their best to order only a few blood tests depending on the needs of the premature babies. Since premature infants cannot form new red blood cells as fast as they are being removed, they sometimes become anemic. Anemia is measured by the level of hemoglobin in the blood and blood transfusions are given when hemoglobin falls below a certain level. It is routine to receive blood transfusions at hemoglobin levels based on your doctor's choice. We have found that some doctors

tend to use the higher levels and some doctors tend to use the lower levels. This study is being conducted because we do not know at which level of hemoglobin it is better to give a premature baby a transfusion. You and your child are being asked to participate in this study to help answer the question, "What is the best level of hemoglobin for transfusing babies in order to achieve the best long term outcome with the fewest risks?"

The purpose of this study is to evaluate if higher hemoglobin levels for transfusing extremely-low-birth-weight infants leads to better outcomes, including survival and development, in infants at 22-26 months adjusted age.

5. ELIGIBILITY

Who is being asked to participate in this research study?

We are asking parents of extremely low birth weight infants (≤1000 grams) and a gestational age of less than 29 weeks to participate.

How long will my baby be in the study? How many other babies will be 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 22-26 month follow-up appointment will be conducted at Women and Children's Hospital Robert Warner Center.

This study will enroll 1824 babies from across the country (approximately 50 babies in Buffalo).

6. PROCEDURES

What procedures will be performed for research purposes?

If you agree to have your baby participate in the study, the following things will happen:

1. Your baby will be randomized into one of two study groups described below. Randomization means that the group is chosen by chance, like flipping a coin. One group will be on a liberal red blood cell transfusion schedule (transfused at a higher hemoglobin level) and the other will be on a more restricted transfusion schedule (transfused at a lower hemoglobin level). Both of these levels are in the standard range used by doctors in Neonatal Intensive Care Units across the country.

   If you have a multiple birth, each baby will be randomized independently and may be assigned to a different study group.

2. While in the hospital, your baby will follow the transfusion group they have been assigned to for all transfusions. If your baby were to get unexpectedly ill or have an unexpected urgent need for blood transfusion, your baby would get the transfusion regardless of the level of hemoglobin.

3. The research team will review certain parts of your baby's medical record and collect information about your baby's growth, test results, and other medical conditions. We will also ask you to complete an economic questionnaire that will provide us with information as to how families cope with having a baby in the Neonatal Intensive Care Unit.

4. At 22-26 months adjusted age, we will ask you to bring your baby back in for a follow-up appointment. At this visit, we will perform a physical test to measure vision and hearing. We will also observe how well your child has learned to walk, talk and play. We will ask you to complete a short questionnaire about how your life and work has been impacted by your baby's stay in the hospital.

7. RISKS

What are the possible risks, side effects, and discomforts of participating in this research study?

Your baby has been born very early, and is at risk for complications of extreme prematurity, such as lung disease, visual problems, developmental delays, and in some cases, death. There are no extra blood tests being done on your baby. Transfusions are routinely performed as standard of care for premature babies and are nowadays extremely safe. The risks associated with this study are exactly the same risks that exist in current medical practice and in blood transfusion therapy. We will ask you to sign a separate consent form for blood transfusions that list possible risks of any transfusion including: infection, volume overload, respiratory deterioration, delay in closure of a blood vessel in the heart that should normally close following birth (patent ductus arteriosus – PDA), and transfusion reactions. Some recent studies have also reported an increased risk of necrotizing enterocolitis (a serious condition of the intestine) following blood transfusions.

Previous studies have shown possible risks associated with both higher and lower thresholds for transfusions: These risks are as follows:

Possible risks with transfusions done to keep your baby's hemoglobin at a higher level include:

If your baby is randomized to the high group it may result not only in more blood transfusions, but the babies may take longer to mature their own bone marrow to produce their own blood. Increased administration of fluids may delay closure of the PDA. An increased number of transfusions may result in a higher amount of iron in your baby's body. Too much iron may increase the risk of chronic lung disease (also called BPD), retinopathy of prematurity (an eye problem in premature infants) or necrotizing enterocolitis. If your baby's care team is worried about excess iron, blood tests will be done, and if the iron level is high, they can decide to not give your baby a transfusion.

Possible risks with transfusions done to keep your baby's hemoglobin at a lower level include:

If your baby is randomized to the low group, they will receive fewer transfusions. A baby with a low hemoglobin level could lead to the baby not having enough hemoglobin to carry oxygen around the body. The frequency of apnea of prematurity may be increased, and weight gain may be slower.

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.

In addition, there are risks of stress, emotional distress, inconvenience and possible loss of privacy and confidentiality associated with participating in a research study. Every effort will be made to keep your baby's medical record strictly confidential. There will be no patient identification in any study report that may be published later on.

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.

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.
During the entire study, an independent committee will review this study to make sure that it continues to be safe.

8. BENEFITS

What are the possible benefits to taking part in this research study?

There may be no direct benefit to your baby from participating in this study. It is our hope that the information gained from this study will help in the treatment of future babies born prematurely.

9. ALTERNATIVES TO PARTICIPATION IN THE RESEARCH STUDY

Are there any other choices available to my child if I decide not to give permission for his/her participation in this study?

If you choose not to participate in this study and if your baby needs a blood transfusion, the doctor will decide at which level of hemoglobin to use in making the decision to transfuse your baby.

10. NEW FINDINGS

Will I be told of any new information or new risks that may be found during the course of this study?

You will be notified of any significant new findings that may cause you to change your mind about having your child participate in this research study.

11. COST ASSOCIATED WITH THE RESEARCH STUDY

Will my child, my child's insurance provider or I be charged for any costs of any procedures performed as part of this research study?

There is no charge to you or your baby for participating in this research. While your baby is in this study, the cost of his/her routine medical care – procedures, medications and doctor visits – will continue to be billed to you or your insurance.

12. REIMBURSEMENT FOR MEDICAL TREATMENT

Who will pay if my child is injured as a result of taking part in this research study?

In the event that this research related activity results in an injury, treatment will be made available including first aid, emergency treatment, and follow-up care as needed. Care for such will be billed in the ordinary manner to you or your insurance company.

Routinely, the Women & Children's Hospital, University at Buffalo Pediatrics, Kaleida Health, Erie County Medical Center, and/or the University at Buffalo, State University of New York, its agents, or its employees do not compensate for or provide free medical care for human subjects in the event that any injury results from participation in a human research project. In the unlikely event that your child becomes ill or injured as a direct result of participating in this study, your child may receive medical care, but it is not the policy of Women & Children's Hospital, University at Buffalo Pediatrics, Kaleida Health, Erie County Medical Center, or the University at Buffalo, State University of New York to provide this care free even if the injury is a direct result of participation.

If you think that your child has suffered research related injury, contact the PI right away at (716) 878-7673.

13. COMPENSATION FOR PARTICIPATION.

Will my child be paid for participating in this study?

You will receive a $60 gift card after completing the 22 to 26 month follow-up visit. We will cover the cost of travel to the WCHOB follow up clinic, if needed.

14. CONFIDENTIALITY

Who will know about my child's participation in this research study?

Information related to your child will be treated in strict confidence to the extent provided by law. Your child's identity will be coded and will not be associated with any published results. Your child's code number and identity will be kept in a locked file of the Principal Investigator. In order to monitor this research study, representatives of the Children & Youth Institutional Review Board (CYIRB) or representatives from federal agencies such as OHRP (Office of Human Research Protection) or NIH (National Institutes of Health) may inspect the research records which may reveal your child's identity.

As required by US law, this clinical trial will be available on http://www.ClinicalTrials.gov with the identifier of NCT01702805. This website will not include information that can identify your child. At most, the website will include a summary of the results. You can search this website at any time.

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 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 Women and Children's Hospital of Buffalo. 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 Kaleida Health workforce members that are not part of the research team. Information within your EMR may also be shared with others who are determined by Kaleida to be appropriate to have access to your EMR (e.g. health insurance company, disability provider, etc).

15. FREEDOM TO WITHDRAW

Is my child's participation in this research study voluntary?

Your child's participation in this study is voluntary and you may withdraw your permission for his/her participation at any time without prejudice and without affecting his/her future health care.

If you choose to withdraw your child from this research study, no further information will be collected from your child or about your child. You should know, however, that the information collected about your child up to the time of your child's withdrawal may continue to be used.

16. REMOVAL FROM STUDY

Can my child be removed from the study without my consent?

It is possible that your child may be removed from the research study by the researchers if, for example the primary investigator feels it is necessary for your baby's health or safety.

If the investigator withdraws your child from the study, no further information will be collected from your child or about your child. You should know, however, that the information collected about your child up to the time of your child's withdrawal may continue to be used.

17. Authorization for the Use and Disclosure of Identifiable Health Information for Research Purposes

This section describes information about your child and about your child's health that will be obtained by the researchers when he/she participates in the research study. Health information is considered "protected health information" when it may directly identify an individual. By signing this form you are agreeing to permit the researchers and/or other parties (described in detail below) to have access to this information about your child. If there are any parts of this form that you do not understand, please be sure to ask us for further clarification.

A. What protected health information will be collected about your child as part of this research study?

__X__ Information from your child's full medical records

__X__ New Health Information created from study related tests, procedures, visits, and/or questionnaires as described in this consent form.

General description of information that will be collected: Blood test results, treatments, physical parameters, diagnosis, transfusions, and therapies.

__X__ Hospital costs

B. Who is authorized to provide or collect this information?

__X__ Principal Investigator or designee

C. With whom may your child's protected health information be shared?

Your child's health information may be shared with others outside of the research group for purposes directly related to the conduct of this research study or as required by law, including but not limited to:

__X__ Clinical staff not involved in this research study who may become involved in your child's care if it is potentially relevant to his/her treatment
__X__ The sponsor of this research study the Eunice Kennedy Shriver NICHD Neonatal Research Network (NRN) or its agents: the standing NRN Data Safety Monitoring Committee
__X__ The organization(s) responsible for administering this research: Neonatal Research Network, the DCC, CYIRB, and the NICHD.
__X__ Other medical investigators/centers/institutions participating in this research study:

University at Buffalo/University of Rochester, NY
Case Western Reserve University, Cleveland, OH
University of Texas-Dallas, TX
Wayne State University, Detroit, MI
Emory University, Atlanta, GA

University of Cincinnati, Cincinnati, OH
Indiana University, Indianapolis, IN
Brown University, Providence, RI
Stanford University, Palo Alto, CA
University of Alabama, Birmingham, AL
University of Texas -Houston, TX
Duke University, Durham, NC
University of Iowa, Iowa City, IA
University of New Mexico, NM
University of Pennsylvania, PA
University of California at Los Angeles, CA
Nationwide Children's Hospital, Columbus, OH
Children's Mercy Hospital, Kansas City, MO

Your child's information may also be shared with individuals or entities responsible for general administration, oversight and compliance of research activities. Examples of this include the institution's Privacy and Security Officers or other internal oversight staff, Safety Monitoring Boards, an Institutional Review Board, The Research Foundation of the State University of New York, University at Buffalo Foundation Services, and accrediting bodies, or with certain government oversight agencies that have authority over the research including the Department of Health and Human Services (HHS), the Food and Drug Administration (FDA), the National Institutes of Health (NIH), and the Office of Human Research Protections (OHRP). Your child's information may also be shared with other entities as permitted or required by law. All reasonable efforts will be used to protect the confidentiality of your child's individually identifiable health information that may be shared with others as described above.

All reasonable efforts will be used to protect the confidentiality of your child's protected health information. There is the potential for individually identifiable information and the associated health information obtained with this authorization to be re-disclosed by the recipient(s). After such a disclosure, the information may no longer be protected by the terms of this authorization against further re-disclosure.

D. How long will this information be kept by the Principal Investigator?

__X__ a. This authorization has no expiration date. The researchers may continue to rely on this authorization to obtain and use protected health information about your child unless you revoke this authorization in writing.

__X__ d. Your child's protected health information will go into a database that will be maintained indefinitely. Any future study using this information that falls outside the scope of this current study will be required to follow guidelines designed to govern access to that information and to protect the privacy of that information.

E. What are your rights after signing this authorization?

You have the right to revoke this authorization at any time. If you withdraw your authorization, no additional efforts to collect individually identifiable health information about your child will be made. You should know, however, that protected health information acquired using this authorization prior to its withdrawal may continue to be used to the extent that the investigator(s) have already relied on your permission to conduct the research. If you choose to withdraw this authorization, you must do so in writing to the following individual(s):

Dr. Satyan Lakshminrusimha
Department of Pediatrics, Division of Neonatology
The Women and Children's Hospital of Buffalo
219 Bryant Street
Buffalo, NY 14222

If you send us a request to withdraw this authorization, we will forward that request to the institutions we have shared it with in order to collect your child's individually identifiable health information.

F. What will happen if you decide not to sign this authorization?

Refusing to sign this authorization will not affect the present or future care your child receives at this institution and will not cause any penalty or loss of benefits to which your child is otherwise entitled. If you decide not to sign this authorization, your child will not be able to participate in the research study.

University at Buffalo
Children & Youth Institutional Review Board (CYIRB)
Women & Children's Hospital of Buffalo
219 Bryant Street – Buffalo, NY 14222

Signature Page

Parental Permission:
All of the above has been explained to me and all of my current questions have been answered. I am encouraged to ask questions about any aspects of this research study before signing this document. If, in the future, I have questions, concerns, or complaints about the research, I should contact:

Name: _ Dr. Satyan Lakshminrusimha _ Title: Principle Investigator Phone Number: (716) 878-7673

If I have any questions, concerns, or complaints about my child's rights as a research participant or want to speak to someone not associated with the research, I should contact the Office of Administration at the Women & Children's Hospital: (716) 878-7551 or 878-7981.

By signing this form I do not waive any of my child's legal rights.
By signing this form, I voluntarily give permission for my child to participate in this research study.

Parental Permission:

PRINT: Name of Child: _____

PRINT: Name of Parent/Legal Guardian: _____

_____ _____
SIGNATURE: Parent/Legal Guardian's signature DATE

Certification of Person Obtaining Consent:
I certify that the nature and purpose, the potential benefits and possible risks associated with participation in this research study have been explained to the above individuals and that any questions about this information have been answered. A copy of this consent will be given to the parent/guardian.

(Print) Name of **Person Obtaining** (PI or Designee)	Signature of Person Obtaining Consent (PI or Designee)	Date

Certification of Witness
I certify that the individuals named above as "Parent(s)/guardian," "Participant" and "Person obtaining consent/permission/assent" signed this document in my presence.

(Print) Name of Witness	Signature of **Witness**	Date

Certification of Principal Investigator:
I certify that the "Person Obtaining Parental Permission/Assent" is an authorized "Designee"

(Print) Name of **Principal Investigator**	Signature of **Principal Investigator**	Date

Study Consent Version Date: April 25, 2013

Parent's Initials: _____

University at Buffalo
Children & Youth IRB Approval
From 5/2/2013 To 3/5/2014

University at Buffalo
Children & Youth Institutional Review Board (CYIRB)
Women & Children's Hospital of Buffalo
219 Bryant Street – Buffalo, NY 14222

Parental Permission to Participate in a Research Study

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?

Short Title: Transfusion of Prematures (TOP)

It is a principle of medical ethics that the subjects of a research project be informed about the research before giving their consent to participate.

You are being asked to give permission for your child to participate in a research study. The purpose of this document is to provide you with information so you can decide whether to give permission for your child to participate in this research study. Your permission should be given based on your understanding of the purpose and benefits of the treatment, device, or procedures that are being used, any potential risks of participation, and whether treatment or compensation is available for physical injuries that result from research procedures. Your decision to give permission for your child to participate in this research is voluntary. If you choose not to give permission for your child to participate in this study or choose to withdraw him/her from the research project at any time, it will have no effect on the quality of his/her future medical care. Please ask questions if there is anything that you do not understand. You have the right to ask for additional information at any time.

1. INVESTIGATOR(S) CONDUCTING THE STUDY

Who is conducting the study?

Dr. Satyan Lakshminrusimha
Dr. Anne Marie Reynolds
Dr. Vivien Carrion
Dr. Corinne Leach
Dr. Vasanth Kumar
Dr. Bobby Mathew
Dr. Sfurti Nath
Dr. Jayasree Nair
Dr. Devaraj Sambalingam
Dr. Vinay Sharma
Dr. Valerie Elberson

Site Principal Investigator:
Satyan Lakshminrusimha, MD
Division of Neonatology
Women and Children's Hospital of Buffalo
219 Bryant Street
Buffalo, NY 14222
Phone: 716-878-7673

Principal Investigator:
Haresh Kirpalani, BM, MSc
Division of Neonatology and Newborn Services
Hospital of the University of Philadelphia
34th and Spruce Street
Philadelphia, PA 19104
Phone: 215-662-3228

Study Consent Version Date: January 30, 2013

Parent's Initials: _____

2. SOURCE OF SUPPORT

Who is sponsoring the research project?

Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), a branch of the National Institute of Health

3. SITES OF THE RESEARCH STUDY

Where will the study take place?

University at Buffalo/University of Rochester, NY
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Wayne State University, Detroit, MI
Emory University, Atlanta, GA
University of Cincinnati, Cincinnati, OH
Indiana University, Indianapolis, IN
Brown University, Providence, RI
Stanford University, Palo Alto, CA
University of Alabama, Birmingham, AL
University of Texas -Houston, TX
Duke University, Durham, NC
University of Iowa, Iowa City, IA
University of New Mexico, NM
University of Pennsylvania, PA
University of California at Los Angeles, CA
Nationwide Children's Hospital, Columbus, OH
Children's Mercy Hospital, Kansas City, MO

4. PURPOSE OF THE RESEARCH STUDY

What is the purpose of the research study?

Doctors and nurses need a better understanding of when we should transfuse blood (as red blood cells) into the blood of premature infants. We know that 90% of babies like yours receive at least one blood transfusion during their stay in the intensive care unit. Blood contains red blood cells, which carry a molecule called 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 how many red blood cells are circulating in your baby's body. Because premature babies need intensive care, they require a lot of blood tests to monitor their care. Doctors try their best to order only a few blood tests depending on the needs of the premature babies. Since premature infants cannot form new red blood cells as fast as they are being removed, they sometimes become anemic. Anemia is measured by the level of hemoglobin in the blood and blood transfusions are given when hemoglobin falls below a certain level. It is routine to receive blood transfusions at hemoglobin levels based on your doctor's choice. We have found that some doctors tend to use the higher levels and some doctors tend to use the lower levels. This is because at the moment, no one knows which level of hemoglobin is better. This study has been designed to gather information to

understand whether higher hemoglobin levels or lower hemoglobin levels lead to improvement in survival and rates of developmental delay in infants at 22-26 months adjusted age.

5. ELIGIBILITY

Who is being asked to participate in this research study?

We are asking parents of extremely low birth weight infants (≤1000 grams) and a gestational age of less than 29 weeks to participate.

How long will my baby be in the study? How many other babies will be 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 22-26 month follow-up appointment will be conducted at Women and Children's Hospital Robert Warner Center.

This study will enroll 1824 babies from across the country (approximately 50 babies in Buffalo).

6. PROCEDURES

What procedures will be performed for research purposes?

If you agree to have your baby participate in the study, the following things will happen:

1. Your baby will be randomized into one of two study groups described below. Randomization means that the group is chosen by chance, like flipping a coin. One group will be on a liberal red blood cell transfusion schedule (transfused at a higher hemoglobin level) and the other will be on a more restricted transfusion schedule (transfused at a lower hemoglobin level). Both of these levels are in the standard range used by doctors in Neonatal Intensive Care Units across the country.

   If you have a multiple birth, each baby will be randomized independently and may be assigned to a different study group.

2. While in the hospital, your baby will follow the transfusion group they have been assigned to for all transfusions. If your baby were to get unexpectedly ill or have an unexpected urgent need for blood transfusion, your baby would get the transfusion regardless of the level of hemoglobin.

3. The research team will review certain parts of your baby's medical record and collect information about your baby's growth, test results, and other medical conditions. We will also ask you to complete an economic questionnaire that will provide us with information as to how families cope with having a baby in the Neonatal Intensive Care Unit.

4. At 22-26 months adjusted age, we will ask you to bring your baby back in for a follow-up appointment. At this visit, we will perform a physical test to measure vision and hearing. We will also observe how well your child has learned to walk, talk and play. We will ask you to complete

a short questionnaire about how your life and work has been impacted by your baby's stay in the hospital.

7. RISKS

What are the possible risks, side effects, and discomforts of participating in this research study?

This study does not carry any additional risks to your baby if you choose to take part. There are no extra blood tests being done on your baby. All transfusions are done as routine standard of care at your doctor's request. This study does not alter the routine care for your baby. The risks associated with this study are exactly the same risks that exist in current medical practice and in blood transfusion therapy. If your baby needs blood for emergency reasons, they will get the blood they need – irrespective of the study. After that urgent need is over, they will then return to the study protocol.

Blood transfusions are nowadays, in general extremely safe. It is simply that giving blood transfusions at too high a hemoglobin level may result not only in more blood transfusions, but the babies may take longer to mature their own bone marrow to produce their own blood. On the other hand, transfusing at too low a hemoglobin level could lead to the baby not having enough hemoglobin to carry oxygen around the body. We avoid these extremes by transfusing within the range of hemoglobin levels that doctors already use.

During the entire study, an independent committee will review this study to make sure that it continues to be safe.

8. BENEFITS

What are the possible benefits to taking part in this research study?

There may be no direct benefit to your baby from participating in this study. It is our hope that the information gained from this study will help in the treatment of future babies born prematurely.

9. ALTERNATIVES TO PARTICIPATION IN THE RESEARCH STUDY

Are there any other choices available to my child if I decide not to give permission for his/her participation in this study?

If you choose not to participate in this study and if your baby needs a blood transfusion, the doctor will decide at which level of hemoglobin to use in making the decision to transfuse your baby.

10. NEW FINDINGS

Will I be told of any new information or new risks that may be found during the course of this study?

You will be notified of any significant new findings that may cause you to change your mind about having your child participate in this research study.

11. COST ASSOCIATED WITH THE RESEARCH STUDY

Will my child, my child's insurance provider or I be charged for any costs of any procedures performed as part of this research study?

There is no charge to you or your baby for participating in this research. While your baby is in this study, the cost of his/her routine medical care – procedures, medications and doctor visits – will continue to be billed to you or your insurance.

12. REIMBURSEMENT FOR MEDICAL TREATMENT

Who will pay if my child is injured as a result of taking part in this research study?

In the event that this research related activity results in an injury, treatment will be made available including first aid, emergency treatment, and follow-up care as needed. Care for such will be billed in the ordinary manner to you or your insurance company.

Routinely, the Women & Children's Hospital, University at Buffalo Pediatrics, Kaleida Health, Erie County Medical Center, and/or the University at Buffalo, State University of New York, its agents, or its employees do not compensate for or provide free medical care for human subjects in the event that any injury results from participation in a human research project. In the unlikely event that your child becomes ill or injured as a direct result of participating in this study, your child may receive medical care, but it is not the policy of Women & Children's Hospital, University at Buffalo Pediatrics, Kaleida Health, Erie County Medical Center, or the University at Buffalo, State University of New York to provide this care free even if the injury is a direct result of participation.

If you think that your child has suffered research related injury, contact the PI right away at (716) 878-7673.

13. COMPENSATION FOR PARTICIPATION.

Will my child be paid for participating in this study?

You will receive a $60 gift card after completing the 22 to 26 month follow-up visit. We will cover the cost of travel to the WCHOB follow up clinic, if needed.

14. CONFIDENTIALITY

Who will know about my child's participation in this research study?

Information related to your child will be treated in strict confidence to the extent provided by law. Your child's identity will be coded and will not be associated with any published results. Your child's code number and identity will be kept in a locked file of the Principal Investigator. In order to monitor this research study, representatives of the Children & Youth Institutional Review Board (CYIRB) or representatives from federal agencies such as OHRP (Office of Human Research Protection) or NIH (National Institutes of Health) may inspect the research records which may reveal your child's identity.

As required by US law, this clinical trial will be available on http://www.ClinicalTrials.gov with the identifier of NCT01702805. This website will not include information that can identify your child. At most, the website will include a summary of the results. You can search this website at any time.

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 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 Women and Children's Hospital of Buffalo. 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 Kaleida Health workforce members that are not part of the research team. Information within your EMR may also be shared with others who are determined by Kaleida to be appropriate to have access to your EMR (e.g. health insurance company, disability provider, etc).

15. FREEDOM TO WITHDRAW

Is my child's participation in this research study voluntary?

Your child's participation in this study is voluntary and you may withdraw your permission for his/her participation at any time without prejudice and without affecting his/her future health care.

If you choose to withdraw your child from this research study, no further information will be collected from your child or about your child. You should know, however, that the information collected about your child up to the time of your child's withdrawal may continue to be used.

16. REMOVAL FROM STUDY

Can my child be removed from the study without my consent?

It is possible that your child may be removed from the research study by the researchers if, for example the primary investigator feels it is necessary for your baby's health or safety.

If the investigator withdraws your child from the study, no further information will be collected from your child or about your child. You should know, however, that the information collected about your child up to the time of your child's withdrawal may continue to be used.

17. Authorization for the Use and Disclosure of Identifiable Health Information for Research Purposes

This section describes information about your child and about your child's health that will be obtained by the researchers when he/she participates in the research study. Health information is considered

"protected health information" when it may directly identify an individual. By signing this form you are agreeing to permit the researchers and/or other parties (described in detail below) to have access to this information about your child. If there are any parts of this form that you do not understand, please be sure to ask us for further clarification.

A. What protected health information will be collected about your child as part of this research study?

__X__ Information from your child's full medical records

__X__ New Health Information created from study related tests, procedures, visits, and/or questionnaires as described in this consent form.

General description of information that will be collected: Blood test results, treatments, physical parameters, diagnosis, transfusions, and therapies.

__X__ Hospital costs

B. Who is authorized to provide or collect this information?

__X__ Principal Investigator or designee

C. With whom may your child's protected health information be shared?

Your child's health information may be shared with others outside of the research group for purposes directly related to the conduct of this research study or as required by law, including but not limited to:

__X__ Clinical staff not involved in this research study who may become involved in your child's care if it is potentially relevant to his/her treatment
__X__ The sponsor of this research study the Eunice Kennedy Shriver NICHD Neonatal Research Network (NRN) or its agents: the standing NRN Data Safety Monitoring Committee
__X__ The organization(s) responsible for administering this research: Neonatal Research Network, the DCC, CYIRB, and the NICHD.
__X__ Other medical investigators/centers/institutions participating in this research study:

University at Buffalo/University of Rochester, NY
Case Western Reserve University, Cleveland, OH
University of Texas-Dallas, TX
Wayne State University, Detroit, MI
Emory University, Atlanta, GA
University of Cincinnati, Cincinnati, OH
Indiana University, Indianapolis, IN
Brown University, Providence, RI

Stanford University, Palo Alto, CA
University of Alabama, Birmingham, AL
University of Texas -Houston, TX
Duke University, Durham, NC
University of Iowa, Iowa City, IA
University of New Mexico, NM
University of Pennsylvania, PA
University of California at Los Angeles, CA
Nationwide Children's Hospital, Columbus, OH
Children's Mercy Hospital, Kansas City, MO

Your child's information may also be shared with individuals or entities responsible for general administration, oversight and compliance of research activities. Examples of this include the institution's Privacy and Security Officers or other internal oversight staff, Safety Monitoring Boards, an Institutional Review Board, The Research Foundation of the State University of New York, University at Buffalo Foundation Services, and accrediting bodies, or with certain government oversight agencies that have authority over the research including the Department of Health and Human Services (HHS), the Food and Drug Administration (FDA), the National Institutes of Health (NIH), and the Office of Human Research Protections (OHRP). Your child's information may also be shared with other entities as permitted or required by law. All reasonable efforts will be used to protect the confidentiality of your child's individually identifiable health information that may be shared with others as described above.

All reasonable efforts will be used to protect the confidentiality of your child's protected health information. There is the potential for individually identifiable information and the associated health information obtained with this authorization to be re-disclosed by the recipient(s). After such a disclosure, the information may no longer be protected by the terms of this authorization against further re-disclosure.

D. How long will this information be kept by the Principal Investigator?

__X_ a. This authorization has no expiration date. The researchers may continue to rely on this authorization to obtain and use protected health information about your child unless you revoke this authorization in writing.

__X__ d. Your child's protected health information will go into a database that will be maintained indefinitely. Any future study using this information that falls outside the scope of this current study will be required to follow guidelines designed to govern access to that information and to protect the privacy of that information.

E. What are your rights after signing this authorization?

You have the right to revoke this authorization at any time. If you withdraw your authorization, no additional efforts to collect individually identifiable health information about your child will be made. You should know, however, that protected health information acquired using this authorization prior to its

withdrawal may continue to be used to the extent that the investigator(s) have already relied on your permission to conduct the research. If you choose to withdraw this authorization, you must do so in writing to the following individual(s):

Dr. Satyan Lakshminrusimha

Department of Pediatrics, Division of Neonatology
The Women and Children's Hospital of Buffalo

219 Bryant Street
Buffalo, NY 14222

If you send us a request to withdraw this authorization, we will forward that request to the institutions we have shared it with in order to collect your child's individually identifiable health information.

F. What will happen if you decide not to sign this authorization?

Refusing to sign this authorization will not affect the present or future care your child receives at this institution and will not cause any penalty or loss of benefits to which your child is otherwise entitled. If you decide not to sign this authorization, your child will not be able to participate in the research study.

Signature Page

Parental Permission:
All of the above has been explained to me and all of my current questions have been answered. I am encouraged to ask questions about any aspects of this research study before signing this document. If, in the future, I have questions, concerns, or complaints about the research, I should contact:

Name: _ Dr. Satyan Lakshminrusimha _ Title __Principal Investigator__
Phone Number: (716) 878-7673

If I have any questions, concerns, or complaints about my child's rights as a research participant or want to speak to someone not associated with the research, I should contact the Office of Administration at the Women & Children's Hospital: (716) 878-7551 or 878-7981.

By signing this form I do not waive any of my child's legal rights.
By signing this form, I voluntarily give permission for my child to participate in this research study.

Parental Permission:

PRINT: Name of Child: _____

University at Buffalo
Children & Youth Institutional Review Board (CYIRB)
Women & Children's Hospital of Buffalo
219 Bryant Street – Buffalo, NY 14222

PRINT: Name of Parent/Legal Guardian: _____

_____ _____
SIGNATURE: Parent/Legal Guardian's signature DATE

Certification of Person Obtaining Consent:
I certify that the nature and purpose, the potential benefits and possible risks associated with participation in this research study have been explained to the above individuals and that any questions about this information have been answered. A copy of this consent will be given to the parent/guardian.

_____ _____ _____
(Print) Name of **Person Obtaining Consent** (PI or Designee) Signature of Person Obtaining Consent (PI or Designee) Date

Certification of Witness
I certify that the individuals named above as "Parent(s)/guardian," "Participant" and "Person obtaining consent/permission/assent" signed this document in my presence.

_____ _____ _____
(Print) Name of Witness Signature of **Witness** Date

Certification of Principal Investigator:
I certify that the "Person Obtaining Parental Permission/Assent" is an authorized "Designee"

_____ _____ _____
(Print) Name of **Principal Investigator** Signature of **Principal Investigator** Date

UNIVERSITY of ROCHESTER MEDICAL CENTER

MEDICINE of THE HIGHEST ORDER

PERMISSION FORM

Transfusion of Prematures 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?

Principal Investigator: **Ronnie Guillet, MD, PhD**
Co-Investigator: **Melissa Carmen, MD**
Carl D'Angio, MD

This permission form describes a research study, what you may expect if you decide to allow your child to take part and important information to help you make your decision. Please read this form carefully.

The study staff will explain this study to you. Please ask questions about anything that is not clear before you decide whether or not you and your child want to participate. You may take this permission form home to think about and discuss with family or friends.

- Being in this study is voluntary – it is your choice.
- If you decide to allow your child to be in the study, you can change your mind and stop at any time.
- If you choose not to take part, your child's medical care will not be changed in any way.
- There are risks from participating and you should understand what these mean to you and your child.

Introduction

Blood contains red cells, which carry a molecule called hemoglobin. Hemoglobin is essential for life as it carries oxygen around the body. Hemoglobin is used by doctors as a measure of how many red blood cells are circulating in your child's body.

Because premature infants need intensive care, they often need a lot of blood tests to monitor their care. Doctors try their best to only order a few blood tests depending on the needs of the premature baby. Because they cannot form new blood cells as fast as they are being removed, very premature babies can become anemic (a low level of hemoglobin). When hemoglobin falls below a certain level, the doctors will transfuse the baby's blood. We know that 90% of babies like yours receive at least one blood transfusion during their stay in the intensive care unit.

This study is being conducted because we do not know at which level of hemoglobin it is better to give a premature baby a transfusion. You and your child are being asked to participate in this study to help answer the question, "What is the best level of hemoglobin for transfusing babies in order to achieve the best long term outcome with the fewest risks for your baby?"

This study is being conducted by Drs. Ronnie Guillet, Melissa Carmen, and Carl D'Angio of the University of Rochester's Department of Pediatrics, Division of Neonatology, in collaboration with the National Child Health and Human Development (NICHD) Neonatology Research Network.

Purpose of Study

The purpose of this study is to help us understand at which level of hemoglobin we should transfuse for the best results.

Description of Study Procedures

If you decide to have your baby participate this study, your baby will be randomly assigned (like a flip of a coin) to either the higher level of hemoglobin or the lower level. Both of these levels are within the usual range used by doctors in the NICU. The doctor will use the assigned level of hemoglobin to decide when to transfuse the baby.

If by chance, your baby were to become unexpectedly ill or have an unexpected urgent need for blood transfusion (where doctors would routinely give blood), your baby would get the needed transfusion, regardless of the level of hemoglobin he or she was assigned to for transfusion as part of the study. All of the blood tests that are done for this study are part of your baby's regular care, so no additional blood samples will be taken.

During your baby's hospitalization, there is a short questionnaire that we will ask you to complete. This questionnaire will help us understand how families cope with and the economic impact of having a baby in the intensive care nursery. You are free to decline to answer some or all of the questions. If you decide that you do not want to complete the economic questionnaire, this will not affect your baby's study participation or the care that he/she receives in the hospital.

We will also collect information from certain parts of your baby's medical record regarding their hospital stay, the treatments they receive and complications they may experience; as well as information from the hospital 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 current costs of taking care of premature babies in the United States.

We will arrange for your baby to come back for a 22-month follow-up appointment with a developmental specialist. All extremely premature babies are routinely seen in a follow-up clinic to check how well they develop and grow. At this time, we will perform a physical exam and measure your child's vision and hearing. This visit could last 2-3 hours, as we will 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 have been impacted by your baby's stay in the hospital. By signing the consent you are giving us permission to collect the results of these evaluations. You and your child's doctor will be given the results of these tests and they will be explained to you.

Number of Subjects

Approximately 1824 babies from 18 NICHD-Neonatal Research Network Study Centers across the country will take part in this research. Locally, about 120 babies will be enrolled over the course of two and a half years.

Duration of the Study

Your child's participation in the study will last for the duration of his/her hospital admission and until the date of the 22-26 month follow-up appointment. The 22-26 month appointment will be completed with a developmental specialist for the final study visit.

Risks of Participation

The overall risks associated with this study are the same risks that exist in current medical practice and in blood transfusion therapy. 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. Some recent studies have also reported an increased risk of necrotizing enterocolitis (a serious condition of the intestine) following blood transfusions.

Previous studies have shown possible risks associated with both higher and lower thresholds for transfusions.

Possible risks with transfusions done to keep your baby's hemoglobin at a higher level include:

- An increased number of transfusions may result in a higher amount of iron in your baby's body. Too much iron may increase the risk of chronic lung disease (also called BPD), retinopathy of prematurity (an eye problem in premature infants) or necrotizing enterocolitis. If your baby's care team is worried that the routine blood tests we do suggest the iron level may be too high, they can decide to not give your baby a transfusion.
- Babies that get more transfusions may also take longer to produce their own blood.

Possible risks associated with letting your baby's hemoglobin go lower include:

- Your baby may not have enough hemoglobin to carry enough oxygen around the body.
- The frequency of apnea (stop in breathing) in premature babies may be increased.
- Weight gain may be slower.

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. Further information on how we protect your personal information is explained in detail below.

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.

Benefits of Participation

Your child might not benefit from being in this research study. However, your baby may benefit from additional monitoring during the study.

New Study Findings

If we discover anything that might make you change your mind about continuing in the study, we will let you know.

Alternatives to Participation

If you choose not to participate in this study, your child will get standard care transfusions.

Sponsor Support

This study has been approved and funded by the National Heart, Lung and Blood Institute and the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), branches of the National Institutes of Health. The University of Rochester is receiving funds from the NICHD to conduct this study. Information about this study is available on a public registry website (http://clinicaltrials.gov --- Study Identifier: NCT 01702805). This website only provides a summary of the research and its findings, no personal information related to individual participants is posted.

Costs

There will be no cost to you/your child to participate in this study. The costs of any other medications or procedures that are done as part of your baby's regular care will be you and/or

your baby's insurance company's responsibility. You are encouraged to discuss your coverage with your child's insurance provider.

Payments
You will receive a $60 gift card and a developmentally appropriate book or toy for your child's evaluation at the 22-26 month visit. We will also pay for parking, bus, or cab fare for this follow-up visit.

Circumstances for Dismissal
Your baby may be withdrawn from the study by the research team or their clinical care doctor if his/her medical condition changes and further participation might pose a risk to his/her health. We will ask, however, that you bring your baby back at 22-26 months for a final evaluation.

Compensation for Injury
If your baby is directly injured by the clinical procedures solely required to participate in this study, you may need to pay for treatment of your baby's injuries, but you will not be required to pay for emergency medical treatment provided at Strong Memorial Hospital. The University may seek payment for this care from your health insurer or third parties. Decisions regarding care and compensation for any other research related injury will be made on a case-by-case basis.

Confidentiality of Records and Authorization to Use and Disclose Information for Research Purposes
The University of Rochester makes every effort to keep the information collected on your child private. In order to do so, we will keep all study documents strictly confidential. Electronic data will be password-protected and all paper forms will be kept in locked files and in locked offices. Only the PI and study staff will have direct access to these documents. Sometimes, however, researchers need to share information that may identify your child with people that work for the University, regulators or the study sponsor.

If you have never received a copy of the University of Rochester Medical Center (URMC) and Affiliates Notice of Privacy Practices, please ask the investigator for one.

What information may be used and given to others?
The study doctor will get your child's personal and medical information. For example:

- Research records
- Records about phone calls made as part of this research
- Records about your child's study visits
- Past and present medical records related to the study
- Results of medical tests
- Hospital Costs

Who may use and give out information about your child?

- The study doctor and the study staff

- URMC and Affiliates

Your child's information may be given to:

- The Department of Health and Human Services;
- The U.S. Food and Drug Administration (FDA);
- The National Institutes of Health;
- The Neonatal Research Network;
- The Research Triangle Institute;
- The University of Rochester;
- The University of Buffalo.

Why will this information be used and/or given to others?

- to do the research,
- to study the results, and
- to see if the research was done right.

If the results of this study are made public, information that identifies your child will not be used.

What if I decide not to give permission to use and give out my child's health information?
Then your child will not be able to be in this research study.

May I review or copy my child's information?
Yes, but only after the research is over.

How long will this be permission be valid?
This permission will last indefinitely.

May I cancel my permission to use and disclose information?
You may cancel your permission to use and disclose your child's health information at any time. You do this by sending written notice to the study doctor. Upon receiving the written notice, the study team will no longer use or disclose your child's health information and they will not be able to stay in this study. Information that has already been gathered may need to be used and given to others for the validity of the study.

May I withdraw from the study?
If you withdraw your permission for your child to be in the study, no new health information identifying your child will be gathered after that date. Information that has already been gathered may still be used and given to others.

Is my child's health information protected after it has been given to others?
There is a risk that your child's information will be given to others without your permission.

Contact Persons

For more information concerning this research or if you feel that your child's participation has resulted in any research related injury, emotional or physical discomfort please contact: Ronnie Guillet at 585-275-6209 or Ann Marie Scorsone, Health Project Coordinator at 585-275-1521.

Please contact the University of Rochester Research Subjects Review Board at 265 Crittenden Blvd., CU 420315, Rochester, NY 14642-8315, Telephone (585) 276-0005 or toll-free at (877) 449-4441 for the following reasons:

- You wish to talk to someone other than the research staff about your rights as a research subject;
- To voice concerns about the research;
- To provide input concerning the research process;
- In the event the study staff could not be reached.

Voluntary Participation

Taking part in this study is voluntary. Your child is free not to take part or to withdraw at any time, for whatever reason. No matter what decision you and your child make, there will be no penalty or loss of benefit to which you and your child are entitled. In the event that your child withdraws or you withdraw your child from this study, the information your child has already provided will be kept in a confidential manner.

SIGNATURE/DATES

After reading and discussing the information in this permission form you should understand:

- Why this study is being done;
- What will happen during the study;
- Any possible risks and benefits to your child;
- Other options your child may have instead of being in the study;
- How your child's personal information will be protected;
- What to do if you have problems or questions about this study.

Future Contact

We would like your permission to keep in contact with you and your child once you have completed your study participation, in case the analysis shows a need/opportunity for additional follow-up.

☐ Yes, I do agree to be contacted in the future regarding participation in this study.
☐ No, I do not agree to contact in the future.

Parent Permission

I have read (or have had read to me) the contents of this permission form and have been encouraged to ask questions. I have received answers to my questions. I agree to allow my child to participate in this study. I have received (or will receive) a copy of this form for my records and future reference.

_____
Subject Name (Printed by Parent)

_____
Parent/Guardian Name (Printed by Parent/Guardian)

_____ _____
Signature of Subject's Parent/Guardian Date

Person Obtaining Permission

I have read this form to the parent and/or the parent has read this form. I will provide the parent with a signed copy of this permission form. An explanation of the research was given and questions from the parent were solicited and answered to the parent's satisfaction. In my judgment, the parent has demonstrated comprehension of the information. I have given the parent adequate opportunity to read the permission form before signing.

_____
Name and Title (Print)

_____ _____
Signature of Person Obtaining Permission Date Time

UNIVERSITY of ROCHESTER MEDICAL CENTER

MEDICINE of THE HIGHEST ORDER

PERMISSION FORM

Transfusion of Prematures 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?

Principal Investigator: **Ronnie Guillet, MD, PhD**
Co-Investigator: **Carl D'Angio, MD**

This permission form describes a research study, what you may expect if you decide to allow your child to take part and important information to help you make your decision. Please read this form carefully.

The study staff will explain this study to you. Please ask questions about anything that is not clear before you decide whether or not you and your child want to participate. You may take this permission form home to think about and discuss with family or friends.

- Being in this study is voluntary – it is your choice.
- If you decide to allow your child to be in the study, you can change your mind and stop at any time.
- If you choose not to take part, your child's medical care will not be changed in any way.
- There are risks from participating and you should understand what these mean to you and your child.

Introduction

Blood contains red cells, which carry a molecule called hemoglobin. Hemoglobin is essential for life as it carries oxygen around the body. Hemoglobin is used by doctors as a measure of how many red blood cells are circulating in your child's body.

Because premature infants need intensive care, they often need a lot of blood tests to monitor their care. Doctors try their best to only order a few blood tests depending on the needs of the

premature baby. Because they cannot form new blood cells as fast as they are being removed, very premature babies can become anemic (a low level of hemoglobin). When hemoglobin falls below a certain level, the doctors will transfuse the baby's blood. We know that 90% of babies like yours receive at least one blood transfusion during their stay in the intensive care unit.

This study is being conducted because we do not know at which level of hemoglobin it is better to give a premature baby a transfusion. You and your child are being asked to participate in this study to help answer the question, "What is the best level of hemoglobin for transfusing babies?"

This study is being conducted by Drs. Ronnie Guillet and Carl D'Angio of the University of Rochester's Department of Pediatrics, Division of Neonatology, in collaboration with the National Child Health and Human Development (NICHD) Neonatology Research Network.

Purpose of Study

The purpose of this study is to help us understand at which level of hemoglobin we should transfuse for the best results.

Description of Study Procedures

If you decide to have your baby participate this study, your baby will be randomly assigned (like a flip of a coin) to either the higher level of hemoglobin or the lower level. Both of these levels are within the usual range used by doctors in the NICU. The doctor will use the assigned level of hemoglobin to decide when to transfuse the baby.

If by chance, your baby were to become unexpectedly ill or have an unexpected urgent need for blood transfusion (where doctors would routinely give blood), your baby would get the needed transfusion, regardless of the level of hemoglobin he or she was assigned to for transfusion as part of the study. All of the blood tests that are done for this study are part of your baby's regular care, so no additional blood samples will be taken.

During your baby's hospitalization, there is a short questionnaire that we will ask you to complete. This questionnaire will help us understand how families cope with and the economic impact of having a baby in the intensive care nursery. We will also collect information from certain parts of your baby's medical record regarding their hospital stay, the treatments they receive and complications they may experience.

We will arrange for your baby to come back for a 22-month follow-up appointment with a developmental specialist. All extremely premature babies are routinely seen in a follow-up clinic to check how well they develop and grow. At this time, we will perform a physical exam and measure your child's vision and hearing. This visit could last 2-3 hours, as we will 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 have been impacted by your baby's stay in the hospital. By signing the consent you are giving us permission to collect the results of these

evaluations. You and your child's doctor will be given the results of these tests and they will be explained to you.

Number of Subjects
Approximately 1824 babies from 18 NICHD-Neonatal Research Network Study Centers across the country will take part in this research. Locally, about 120 babies will be enrolled over the course of two and a half years.

Duration of the Study
Your child's participation in the study will last for the duration of his/her hospital admission and until the date of the 22-26 month follow-up appointment. The 22-26 month appointment will be completed with a developmental specialist for the final study visit.

Risks of Participation
The risks associated with this study are exactly the same risks that exist in current medical practice and in blood transfusion therapy. If your baby needs blood for emergency reasons, where all doctors would routinely give blood, they will get the blood they need – irrespective of the study. After the urgent need is over, your baby will return to the study protocol.

Blood transfusions are in general extremely safe. Giving blood transfusions at too high a hemoglobin level may result not only in more blood transfusions, but babies may take longer to produce their own blood. On the other hand, transfusing at too low a level of hemoglobin, could lead to babies not having enough hemoglobin to carry enough oxygen around the body. This study avoids these extremes by transfusing within the ranges of hemoglobin level that doctors nowadays already use.

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. Further information on how we protect your personal information is explained in detail below.

Benefits of Participation
Your child might not benefit from being in this research study. However, your baby may benefit from additional monitoring during the study.

New Study Findings
If we discover anything that might make you change your mind about continuing in the study, we will let you know.

Alternatives to Participation
If you choose not to participate in this study, your child will get standard care transfusions.

Sponsor Support
The University of Rochester is receiving funds from the National Institute of Child Health and Human Development, a branch of the National Institutes of Health to conduct this study.

Costs
There will be no cost to you/your child to participate in this study. The costs of any other medications or procedures that are done as part of your baby's regular care will be you and/or your baby's insurance company's responsibility. You are encouraged to discuss your coverage with your child's insurance provider.

Payments
You will receive a $40 gift card and a developmentally appropriate book or toy for your child's evaluation at the 22-26 month visit. We will also pay for parking, bus, or cab fare for this follow-up visit.

Circumstances for Dismissal
Your baby may be withdrawn from the study by the research team or their clinical care doctor if his/her medical condition changes and further participation might pose a risk to his/her health. We will ask, however, that you bring your baby back at 22-26 months for a final evaluation.

Compensation for Injury
If your baby is directly injured by the clinical procedures solely required to participate in this study, you may need to pay for treatment of your baby's injuries, but you will not be required to pay for emergency medical treatment provided at Strong Memorial Hospital. The University may seek payment for this care from your health insurer or third parties. Decisions regarding care and compensation for any other research related injury will be made on a case-by-case basis.

Confidentiality of Records and Authorization to Use and Disclose Information for Research Purposes
The University of Rochester makes every effort to keep the information collected on your child private. In order to do so, we will keep all study documents strictly confidential. Electronic data will be password-protected and all paper forms will be kept in locked files and in locked offices. Only the PI and study staff will have direct access to these documents. Sometimes, however, researchers need to share information that may identify your child with people that work for the University, regulators or the study sponsor.

If you have never received a copy of the University of Rochester Medical Center (URMC) and Affiliates Notice of Privacy Practices, please ask the investigator for one.

What information may be used and given to others?
The study doctor will get your child's personal and medical information. For example:

- Research records
- Records about phone calls made as part of this research

- Records about your child's study visits
- Past and present medical records related to the study
- Results of medical tests

Who may use and give out information about your child?
- The study doctor and the study staff
- URMC and Affiliates

Your child's information may be given to:
- The Department of Health and Human Services;
- The U.S. Food and Drug Administration (FDA);
- The National Institutes of Health;
- The Neonatal Research Network;
- The Research Triangle Institute;
- The University of Rochester;
- The University of Buffalo.

Why will this information be used and/or given to others?
- to do the research,
- to study the results, and
- to see if the research was done right.

If the results of this study are made public, information that identifies your child will not be used.

What if I decide not to give permission to use and give out my child's health information?
Then your child will not be able to be in this research study.

May I review or copy my child's information?
Yes, but only after the research is over.

How long will this be permission be valid?
This permission will last indefinitely.

May I cancel my permission to use and disclose information?
You may cancel your permission to use and disclose your child's health information at any time. You do this by sending written notice to the study doctor. Upon receiving the written notice, the study team will no longer use or disclose your child's health information and they will not be able to stay in this study. Information that has already been gathered may need to be used and given to others for the validity of the study.

May I withdraw from the study?
If you withdraw your permission for your child to be in the study, no new health information identifying your child will be gathered after that date. Information that has already been gathered may still be used and given to others.

Is my child's health information protected after it has been given to others?
There is a risk that your child's information will be given to others without your permission.

Contact Persons

For more information concerning this research or if you feel that your child's participation has resulted in any research related injury, emotional or physical discomfort please contact: Ronnie Guillet at 585-275-6209 or Ann Marie Scorsone, Health Project Coordinator at 585-275-1521.

Please contact the University of Rochester Research Subjects Review Board at 265 Crittenden Blvd., CU 420315, Rochester, NY 14642-8315, Telephone (585) 276-0005 or toll-free at (877) 449-4441 for the following reasons:

- You wish to talk to someone other than the research staff about your rights as a research subject;
- To voice concerns about the research;
- To provide input concerning the research process;
- In the event the study staff could not be reached.

Voluntary Participation

Taking part in this study is voluntary. Your child is free not to take part or to withdraw at any time, for whatever reason. No matter what decision you and your child make, there will be no penalty or loss of benefit to which you and your child are entitled. In the event that your child withdraws or you withdraw your child from this study, the information your child has already provided will be kept in a confidential manner.

SIGNATURE/DATES

After reading and discussing the information in this permission form you should understand:

- Why this study is being done;
- What will happen during the study;
- Any possible risks and benefits to your child;
- Other options your child may have instead of being in the study;
- How your child's personal information will be protected;
- What to do if you have problems or questions about this study.

Future Contact

We would like your permission to keep in contact with you and your child once you have completed your study participation, in case the analysis shows a need/opportunity for additional follow-up.

- ☐ Yes, I do agree to be contacted in the future regarding participation in this study.
- ☐ No, I do not agree to contact in the future.

Parent Permission

I have read (or have had read to me) the contents of this permission form and have been encouraged to ask questions. I have received answers to my questions. I agree to allow my child to participate in this study. I have received (or will receive) a copy of this form for my records and future reference.

_____

Subject Name (Printed by Parent)

_____

Parent/Guardian Name (Printed by Parent/Guardian)

_____ _____

Signature of Subject's Parent/Guardian Date

Person Obtaining Permission

I have read this form to the parent and/or the parent has read this form. I will provide the parent with a signed copy of this permission form. An explanation of the research was given and questions from the parent were solicited and answered to the parent's satisfaction. In my judgment, the parent has demonstrated comprehension of the information. I have given the parent adequate opportunity to read the permission form before signing.

_____

Name and Title (Print)

_____ _____

Signature of Person Obtaining Permission Date

IRB Use Only
Approval Date: March 4, 2013
Expiration Date: December 18, 2013

Is your child participating in any other research studies? _____ yes _____ no

Your child is invited to participate in a research study of whether it is better to give red blood cells (transfusion) to premature infants when their hemoglobin level is higher or when it is lower. Hemoglobin is the molecule in red blood cells that carries oxygen around the body. Most babies born before 29 weeks receive one or more transfusions during their hospital stay. Doctors decide to transfuse when the hemoglobin level falls below a certain level. Currently, it is not known if transfusing a premature infant at a higher or lower hemoglobin level higher is better for outcome. Because it is not known if one approach is better than the other, both approaches are common in the care of premature infants. This study will look to see if there is a difference in complications while in the NICU and a difference in development at 24 months of age, corrected for prematurity, between infants who are transfused at a higher hemoglobin compared to infants who are transfused at a lower hemoglobin.

The purpose of this study is to determine the best level of hemoglobin at which premature infants should be transfused. Your child is eligible to participate because he/she was born before 29 weeks and had a birth weight of 1,000 grams or lower.

This project, funded by the National Institutes of Health, is being conducted at Stanford and 17 other medical centers across the country to determine the best level of hemoglobin for transfusing premature babies. Nationwide, 1824 infants will be enrolled over about 3 years. Up to 100 infants will be enrolled at Stanford. Each child will be involved until about two years of age, corrected for prematurity.

If you decide to allow your child to participate in this project, he/she will be randomly assigned (like the flip of a coin) to receive transfusions when the hemoglobin drops below the higher level or when the hemoglobin drops below the lower level. Your baby has a 50-50 chance of being assigned to each group. Neither you nor the doctors taking care of your child will be able to choose the group to which your infant is assigned. All other care for your child will be the usual intensive care provided to premature infants. When your child is about two weeks old, we will ask you to fill out a short questionnaire that asks about how your life and work may have been affected by your child's stay in the hospital. You have the right to refuse to answer particular questions.

This study will collect information about your child's health including, but not limited to, physical examinations; prenatal and birth records; respiratory records; nursing records; vital signs; medication records; surgeries; blood, urine, and other tissue samples and related records; imaging; nutrition; development; vision; and hearing for the first two years, corrected for prematurity.

Children who are born prematurely are routinely seen in the outpatient Infant Development Clinic at regular intervals until about two years corrected age to assure that growth and development are progressing well. As part of this study, data will be collected from the 22-26 month (corrected age) visit to monitor your child's outcome. The visit consists of a physical exam, review of medical history and medications, and a developmental assessment. It usually

takes about two hours. In order to stay in touch with families during the two-year follow-up phase, study personnel may contact you to check on your child's health and update your contact information. They may also use social media sites to re-establish contact with you if needed.

Your child's participation in this study is entirely voluntary. Your decision not to allow your child to participate will not have any negative effect on your child or his/her medical care. You can decide to let your child participate now but withdraw your consent later and stop your child's participation in the study without any loss of benefits or medical care to which your child is entitled. If you decide to withdraw your child from this study, the use of the study hemoglobin threshold for transfusions will be discontinued and the medical staff will select the hemoglobin level at which your child receives transfusions. If you decide to terminate your child's participation in this study, you should notify Dr. Van Meurs at (650) 723-5711.

The protocol director may withdraw your child from the study and the use of the study hemoglobin level may be stopped without your consent for one or more of the following reasons: the investigator deciding that continued participation could be harmful to your child, the study being canceled, some other administrative reason, or unanticipated circumstances.

This study does not change the routine care for your child. The risks associated with this study are the same risks that exist in current medical practice and in blood transfusion therapy, including the risks of donor exposure and IV placement. If your child needs blood for emergency reasons, where all doctors would routinely give blood, they will get the blood they need – no matter which study group they are in. After the urgent need passes, your child will then return to the study guidelines. A potential risk of this study is the risk to confidentiality. Although the investigator cannot guarantee that your child's records will remain confidential, every effort will be made to keep your child's medical record confidential as required by law. In addition to these, there may be other unknown risks, or risks that the investigators did not anticipate, associated with being in this study.

It is unknown if your child will benefit from participation in this study. There may be some benefit from the extra monitoring that will occur with this study. The information gained from this study may help doctors in the future to select the best level of hemoglobin for transfusing premature babies.

We cannot and do not guarantee or promise that your child will receive any benefit from this study.

The alternative to having your child participate in this project is not to participate.
You should not feel obligated to allow your child to participate in this study. Your questions should be answered clearly and to your satisfaction. If you choose not to have your child participate, tell the protocol director or research staff.

You will be told of any important new information that is learned during the course of this research study that might affect your child's condition or your willingness to have your child continue participation in this study.

A description of this study will be available on http://clinicaltrials.gov, as required by U.S. law. The website will not include information that can identify you or your child. At most, the website will include a summary of the results. You can search the website at any time. This study is registered under the identifier NCT 01702805.

The results of this research study may be presented at scientific or medical meetings or published in scientific journals. However, your child's identity will not be disclosed. Patient information may be provided to Federal and other regulatory agencies as required. The Food and Drug Administration (FDA), for example, may inspect research records and learn your child's identity if this study falls within its jurisdiction.

Your child will not be paid to participate in this research study. There is no cost to your child for participating in this study. The National Institutes of Health (NIH) are providing financial support and/or materials for this study.

All forms of medical diagnosis and treatment – whether routine or experimental – involve some risk of injury. In spite of all precautions, your child might develop medical complications from participating in this study. If such complications arise, the protocol director and the research study staff will assist you in obtaining appropriate medical treatment. In the event that your child has an injury or illness that is directly caused by his/her participation in this study, reimbursement for all related costs of care first will be sought from your or your child's insurer, managed care plan, or other benefits program. You or your child will be responsible for any associated co-payments or deductibles as required by your or his/her insurance. If costs of care related to such an injury are not covered by your child's insurer, managed care plan or other benefits program, you or your child may be responsible for these costs. If you or your child are unable to pay for such costs, the protocol director will assist you in applying for supplemental benefits and explain how to apply for patient financial assistance from the hospital.

You do not waive any liability rights for personal injury by signing this form.

If you have any questions, concerns or complaints about this research study, its procedures, risks and benefits, or alternative courses of treatment, you should ask the protocol director, Dr. Van Meurs at 650 723 5711. You should also contact her at any time if you feel your child has been hurt by being a part of this study. If you cannot reach the protocol director, please call the NICU attending physician at 650 497 8800.

If you are not satisfied with how this study is being conducted or if you have any concerns, complaints, or general questions about the research or your child's rights as a research study participant, please contact the Stanford Institutional Review Board (IRB) to speak to someone independent of the research team at (650) 723-5244 or toll free at (866) 680-2906. You can also write to the Stanford IRB, Stanford University, MC 5579, Palo Alto, CA 94304.
As a research participant your child has the following rights. These rights include but are not limited to the participant's right to:

- be informed of the nature and purpose of the experiment;
- be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be utilized;
- be given a description of any attendant discomforts and risks reasonably to be expected;
- be given an explanation of any benefits to the subject reasonably to be expected, if applicable;
- be given a disclosure of any appropriate alternatives, drugs, or devices that might be advantageous to the subject, their relative risks and benefits;
- be informed of the avenues of medical treatment, if any, available to the subject after the experiment if complications should arise;
- be given an opportunity to ask any questions concerning the experiment or the procedures involved;
- be instructed that consent to participate in the medical experiment may be withdrawn at any time and the subject may discontinue participation without prejudice;
- be given a copy of the signed and dated consent form;
- be given the opportunity to decide to consent or not to consent to a medical experiment without the intervention of any element of force, fraud, deceit, coercion or undue influence on the subject's decision.

Signing your name means you agree to have your child participate in this study and that you were given a copy of this consent form.

Signature of Parent	Date	Authority to act for participant
(If available) Signature of Other Parent	Date	Authority to act for participant

The IRB determined that the permission of one parent is sufficient for research to be conducted under 45 CFR 46.404, in accordance with 45 CFR 46.408(b).

Signature of Person Obtaining Consent	Date

IRB Use Only
Approval Date: March 4, 2013
Expiration Date: December 18, 2013

The following witness line is to be signed only if the consent is provided as a summary form and accompanied by a short form foreign language consent.

_____ _____

Signature of Witness Date

(e.g., staff, translator/interpreter, family member, or other person who speaks both English and the participant's language)

- Translated short form must be signed and dated by both the participant (or their LAR) and the witness.
- The English consent form (summary form) must be signed by the witness and the POC. The non-English speaking participant does not sign the English consent.
- The non-English speaking participant should not sign the HIPAA participant line

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Approval Date: January 22, 2013
Expiration Date: December 18, 2013

Is your child participating in any other research studies? _____ yes _____ no

Your child is invited to participate in a research study of whether it is better to give red blood cells (transfusion) to premature infants when their hemoglobin level is higher or when it is lower. Hemoglobin is the molecule in red blood cells that carries oxygen around the body. Most babies born before 29 weeks receive one or more transfusions during their hospital stay. Doctors decide to transfuse when the hemoglobin level falls below a certain level. Currently, it is not known if transfusing a premature infant at a higher or lower hemoglobin level higher is better for outcome. Because it is not known if one approach is better than the other, both approaches are common in the care of premature infants. This study will look to see if there is a difference in complications while in the NICU and a difference in development at 24 months of age, corrected for prematurity, between infants who are transfused at a higher hemoglobin compared to infants who are transfused at a lower hemoglobin.

The purpose of this study is to determine the best level of hemoglobin at which premature infants should be transfused. Your child is eligible to participate because he/she was born before 29 weeks and had a birth weight of 1,000 grams or lower.

This project, funded by the National Institutes of Health, is being conducted at Stanford and 17 other medical centers across the country to determine the best level of hemoglobin for transfusing premature babies. Nationwide, 1824 infants will be enrolled over about 3 years. Up to 100 infants will be enrolled at Stanford. Each child will be involved until about two years of age, corrected for prematurity.

If you decide to allow your child to participate in this project, he/she will be randomly assigned (like the flip of a coin) to receive transfusions when the hemoglobin drops below the higher level or when the hemoglobin drops below the lower level. Your baby has a 50-50 chance of being assigned to each group. Neither you nor the doctors taking care of your child will be able to choose the group to which your infant is assigned. All other care for your child will be the usual intensive care provided to premature infants. When your child is about two weeks old, we will ask you to fill out a short questionnaire that asks about how your life and work may have been affected by your child's stay in the hospital. You have the right to refuse to answer particular questions.

This study will collect information about your child's health including, but not limited to, physical examinations; prenatal and birth records; respiratory records; nursing records; vital signs; medication records; surgeries; blood, urine, and other tissue samples and related records; imaging; nutrition; development; vision; and hearing for the first two years, corrected for prematurity.

Children who are born prematurely are routinely seen in the outpatient Infant Development Clinic at regular intervals until about two years corrected age to assure that growth and development are progressing well. As part of this study, data will be collected from the 22-26 month (corrected age) visit to monitor your child's outcome. The visit consists of a physical exam, review of medical history and medications, and a developmental assessment. It usually

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takes about two hours. In order to stay in touch with families during the two-year follow-up phase, study personnel may contact you to check on your child's health and update your contact information. They may also use social media sites to re-establish contact with you if needed.

Your child's participation in this study is entirely voluntary. Your decision not to allow your child to participate will not have any negative effect on your child or his/her medical care. You can decide to let your child participate now but withdraw your consent later and stop your child's participation in the study without any loss of benefits or medical care to which your child is entitled. If you decide to withdraw your child from this study, the use of the study hemoglobin threshold for transfusions will be discontinued and the medical staff will select the hemoglobin level at which your child receives transfusions. If you decide to terminate your child's participation in this study, you should notify Dr. Van Meurs at (650) 723-5711.

The protocol director may withdraw your child from the study and the use of the study hemoglobin level may be stopped without your consent for one or more of the following reasons: the investigator deciding that continued participation could be harmful to your child, the study being canceled, some other administrative reason, or unanticipated circumstances.

This study does not change the routine care for your child. The risks associated with this study are the same risks that exist in current medical practice and in blood transfusion therapy. If your child needs blood for emergency reasons, where all doctors would routinely give blood, they will get the blood they need – no matter which study group they are in. After the urgent need passes, your child will then return to the study guidelines. A potential risk of this study is the risk to confidentiality. Although the investigator cannot guarantee that your child's records will remain confidential, every effort will be made to keep your child's medical record confidential as required by law. In addition to these, there may be other unknown risks, or risks that the investigators did not anticipate, associated with being in this study.

It is unknown if your child will benefit from participation in this study. There may be some benefit from the extra monitoring that will occur with this study. The information gained from this study may help doctors in the future to select the best level of hemoglobin for transfusing premature babies.

We cannot and do not guarantee or promise that your child will receive any benefit from this study.

The alternative to having your child participate in this project is not to participate.
You should not feel obligated to allow your child to participate in this study. Your questions should be answered clearly and to your satisfaction. If you choose not to have your child participate, tell the protocol director or research staff.

You will be told of any important new information that is learned during the course of this research study that might affect your child's condition or your willingness to have your child continue participation in this study.

A description of this study will be available on http://clinicaltrials.gov, as required by U.S. law. The website will not include information that can identify you or your child. At most, the website will include a summary of the results. You can search the website at any time. This study is registered under the identifier NCT 01702805.

The results of this research study may be presented at scientific or medical meetings or published in scientific journals. However, your child's identity will not be disclosed. Patient information may be provided to Federal and other regulatory agencies as required. The Food and Drug Administration (FDA), for example, may inspect research records and learn your child's identity if this study falls within its jurisdiction.

Your child will not be paid to participate in this research study. There is no cost to your child for participating in this study. The National Institutes of Health (NIH) are providing financial support and/or materials for this study.

All forms of medical diagnosis and treatment – whether routine or experimental – involve some risk of injury. In spite of all precautions, your child might develop medical complications from participating in this study. If such complications arise, the protocol director and the research study staff will assist you in obtaining appropriate medical treatment. In the event that your child has an injury or illness that is directly caused by his/her participation in this study, reimbursement for all related costs of care first will be sought from your or your child's insurer, managed care plan, or other benefits program. You or your child will be responsible for any associated co-payments or deductibles as required by your or his/her insurance. If costs of care related to such an injury are not covered by your child's insurer, managed care plan or other benefits program, you or your child may be responsible for these costs. If you or your child are unable to pay for such costs, the protocol director will assist you in applying for supplemental benefits and explain how to apply for patient financial assistance from the hospital.

You do not waive any liability rights for personal injury by signing this form.

If you have any questions, concerns or complaints about this research study, its procedures, risks and benefits, or alternative courses of treatment, you should ask the protocol director, Dr. Van Meurs at 650 723 5711. You should also contact her at any time if you feel your child has been hurt by being a part of this study. If you cannot reach the protocol director, please call the NICU attending physician at 650 497 8800.

If you are not satisfied with how this study is being conducted or if you have any concerns, complaints, or general questions about the research or your child's rights as a research study participant, please contact the Stanford Institutional Review Board (IRB) to speak to someone independent of the research team at (650) 723-5244 or toll free at (866) 680-2906. You can also write to the Stanford IRB, Stanford University, MC 5579, Palo Alto, CA 94304.

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As a research participant your child has the following rights. These rights include but are not limited to the participant's right to:

- be informed of the nature and purpose of the experiment;
- be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be utilized;
- be given a description of any attendant discomforts and risks reasonably to be expected;
- be given an explanation of any benefits to the subject reasonably to be expected, if applicable;
- be given a disclosure of any appropriate alternatives, drugs, or devices that might be advantageous to the subject, their relative risks and benefits;
- be informed of the avenues of medical treatment, if any, available to the subject after the experiment if complications should arise;
- be given an opportunity to ask any questions concerning the experiment or the procedures involved;
- be instructed that consent to participate in the medical experiment may be withdrawn at any time and the subject may discontinue participation without prejudice;
- be given a copy of the signed and dated consent form;
- be given the opportunity to decide to consent or not to consent to a medical experiment without the intervention of any element of force, fraud, deceit, coercion or undue influence on the subject's decision.

Signing your name means you agree to have your child participate in this study and that you were given a copy of this consent form.

Signature of Parent	Date	Authority to act for participant
(If available) Signature of Other Parent	Date	Authority to act for participant

The IRB determined that the permission of one parent is sufficient for research to be conducted under 45 CFR 46.404, in accordance with 45 CFR 46.408(b).

Signature of Person Obtaining Consent	Date

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The following witness line is to be signed only if the consent is provided as a summary form and accompanied by a short form foreign language consent.

_____ _____

Signature of Witness Date

(e.g., staff, translator/interpreter, family member, or other person who speaks both English and the participant's language)

- Translated short form must be signed and dated by both the participant (or their LAR) and the witness.
- The English consent form (summary form) must be signed by the witness and the POC. The non-English speaking participant does not sign the English consent.
- The non-English speaking participant should not sign the HIPAA participant line

Authorization To Use Your Child's Health Information For Research Purposes

Because information about your child and his/her health is personal and private, it generally cannot be used in this research study without your written authorization. If you sign this form, it will provide that authorization. The form is intended to inform you about how your child's health information will be used or disclosed in the study. Your child's information will only be used in accordance with this authorization form and the informed consent form and as required or allowed by law. Please read it carefully before signing it.

What is the purpose of this research study and how will my child's health information be utilized in the study?

The study is designed to determine the best level of hemoglobin at which premature infants should be transfused. Your child's health information will be used to compare parameters such as growth, complications in the NICU, and neurodevelopmental outcome at 22-26 months. The information will have your child's study number on it, not his/her name. The results of the study will be published in a scientific or medical journal but the identities of children who were in the study will not be disclosed.

Do I have to sign this authorization form?

You do not have to sign this authorization form. But if you do not, your child will not be able to participate in this research study. Signing the form is not a condition for receiving any medical care outside the study.

If I sign, can I revoke it or withdraw my child from the research later?

If you decide to allow your child to participate, you are free to withdraw your authorization regarding the use and disclosure of your child's health information (and to discontinue any other participation in the study) at any time. After any revocation, your child's health information will no longer be used or disclosed in the study, except to the extent that the law allows us to continue using your information (e.g., necessary to maintain integrity of research). If you wish to revoke your authorization for the research use or disclosure of your child's health information in this study, must write to: Dr. Krisa Van Meurs, Division of Neonatology, Stanford University, 750 Welch Road, Stanford CA 94304.

What Personal Information Will Be Used or Disclosed?

Your child's health information related to this study may be used or disclosed in connection with this research study including, but not limited to, records of: physical examinations; prenatal data and birth; respiration; nursing care; vital signs; medication; surgeries; blood, urine, and other tissue samples; imaging; nutrition; development; vision; and hearing for the first two years of life, corrected for prematurity.

Who May Use or Disclose the Information?

The following parties are authorized to use and/or disclose your child's health information in connection with this research study:

- The Protocol Director, Krisa Van Meurs, MD
- The Assistant Protocol Director, David Stevenson, MD
- The Stanford University Administrative Panel on Human Subjects in Medical Research and any other unit of Stanford University as necessary
- Research staff

Who May Receive or Use the Information?

The parties listed in the preceding paragraph may disclose your child's health information to the following persons and organizations for their use in connection with this research study:

- The Office for Human Research Protections in the U.S. Department of Health and Human Services
- The National Institute of Child Health and Human Development Neonatal Research Network
- Research Triangle Institute (data management center)
- Researchers at other institutions

Your child's information may be re-disclosed by the recipients described above, if they are not required by law to protect the privacy of the information.

When will my authorization expire?

Your authorization for the use and/or disclosure of your child's health information will end on December 31, 2100 or when the research project ends, whichever is earlier.

Will access to my child's medical record be limited during the study?

To maintain the integrity of this research study, you may not have access to any health information developed as part of this study until it is completed. At that point, you would have access to such health information if it was used to make medical or billing decisions about your child (e.g., if included in your child's official medical record).

_____ _____

Signature of Legally Authorized Representative Date

_____

Description of Representative's Authority to Act for Subject

University Of California Los Angeles
Consent to Participate In Research

Transfusion of Prematures (TOP) Trial

To find out the hemoglobin level that will be best for the development and outcome of premature babies after discharge from the NICU

INTRODUCTION

You and your baby are being invited to participate in a research study conducted by Dr. Meena Garg and Dr. Uday Devaskar, from the Division of Neonatology, Department of Pediatrics, at Mattel Children's Hospital, UCLA. Your baby's participation is completely voluntary. Your choice will not affect the medical care that your baby will receive. Your doctors, nurses, and therapists will not treat you differently if you do not participate in this study. The research team will explain this study to you. Please take your time about deciding whether to participate in this study. Before deciding:

- You can discuss this study with friends and family
- You can also discuss it with your baby's doctor or request a second opinion
- If you have any questions, you can ask the researchers for more information before deciding to participate.

The research team is asking you to be in this study because the doctors and nurses need to better understand when we should transfuse blood (as red cells) into the blood of premature infants. Blood contains red cells, which carry a protein called 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 how many red blood cells are circulating in your baby's body.

WHY IS THIS STUDY BEING DONE?

The purpose of this research study is to determine the level of hemoglobin that is best for the outcome of premature babies after discharge from NICU. Premature babies need intensive care and therefore they need a lot of blood tests to monitor their care. Doctors try their best to order only a few blood tests depending on the needs of the premature babies. Since premature babies cannot make red blood cells easily, they sometimes become anemic. Anemia occurs when your blood does not have enough red blood cells or hemoglobin. Therefore, we have to give them blood transfusions.

When the hemoglobin falls below a certain level, doctors will transfuse the baby. However, we know that some doctors tend to use a higher level of hemoglobin and some doctors tend to use a lower level of hemoglobin. The reason for this is that we do not know which level of hemoglobin is better. This study has been designed to help us find out when we should best transfuse babies.

This study has been approved and funded by the National Heart Lung and Blood Institute and the Eunice Kennedy Shriver National Institute of Child Health and Human Development, both are branches of the National Institutes of Health.

HOW MANY BABIES WILL TAKE PART IN THIS STUDY?

100 babies will take part in this study at UCLA. About 1824 babies will participate in this study across 18 large hospitals in the US.

WHAT WILL HAPPEN TO MY BABY IF MY BABY TAKES PART IN THIS STUDY?

Before your baby begins the study:

Babies like yours, who are born extremely premature and who need intensive care, require a lot of blood tests. Because they cannot form new blood cells as fast as they are being removed, very premature babies become anemic and often require blood transfusion. We know that 90% of babies like yours receive at least one blood transfusion during their stay in the intensive care unit.

Anemia is measured by the level of hemoglobin in the blood and blood transfusions are given when hemoglobin falls below a certain level. It is routine to receive blood transfusions at hemoglobin levels based on your doctor's choice. We have found that some doctors tend to use the higher levels and some doctors tend to use the lower levels. This is because at the moment, no one knows which level of hemoglobin is better.

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

This study is trying to provide an answer to the question: "What is the best level of hemoglobin for transfusing babies?"

During the study:

If you agree to have your baby take part in this study, your baby will be randomly assigned (like flipping a coin) to either the higher level of hemoglobin or the lower level. Both of these levels are in the usual range used by doctors in the NICU. Your baby's doctor will use this level of hemoglobin to decide when to transfuse your baby.

If your baby were to get unexpectedly ill or have an urgent need for blood transfusion (e.g. right before going to surgery), your baby would get the transfusion regardless of the level of hemoglobin your baby was assigned to. All of the blood tests that are done are routine standard of care. We will ask you to complete an economic questionnaire that will help provide us with information as to how families cope with having a baby in the intensive care unit.

Collection of information:

This study begins with your agreement to allow your baby to take part. Your baby will be followed in the hospital from birth through discharge. Your baby's hospital course will be followed closely and important information will be gathered such as ventilator (breathing machine) and oxygen requirements, infections, heart problems, feeding difficulties, brain problems, and blood draw results. Information will be collected from the chart prior to enrollment as well as after enrollment until your baby comes to the clinic for his/her 22 -26 month visit. If your baby was not born at a UCLA hospital, we would like your permission to

obtain a copy of his/her medical record from the delivery hospital along with mom's pregnancy and delivery medical notes.

Follow-up visit:
After discharge from the hospital, we will ask to see your baby in the High Risk Infant Follow-Up Clinic at UCLA around 3 months, 6 months, 12 months, and at 22 – 26 months of age. The 22 – 26 month visit is most important. When your child is 22 – 26 months old, he/she will be seen at the Developmental Assessment High Risk Infant Follow-up Clinic at UCLA or at the Clinical & Translational Research Center at UCLA for the follow-up visit. At this 2-3 hour follow-up visit, you will be asked questions about how your child is doing (approximately 30 minutes), a pediatrician will examine your child (approximately 30 minutes) and his/her development will also be checked. Your child will undergo developmental testing by a trained psychologist or tester (lasting about 1 hour). We will also observe how well your child is walking, talking, and playing.

These follow-up visits will be scheduled as part of your baby's standard clinical care. In other words, even if you did not participate in this study, we would ask that we see your baby at 3, 6, 12, and 22 – 26 months of age to follow your baby's progress. We will only be collecting information that is obtained from these visits for the purpose of the research study.

HOW LONG WILL MY BABY BE IN THIS 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.

WHAT KINDS OF RISKS OR DISCOMFORTS COULD I EXPECT?

Known risks and 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 does not carry any additional risks to your baby if you choose to take part. There are no extra blood tests being done on your baby. All blood tests are done as routine standard of care at your doctor's request. The risks associated with this study are exactly the same risks that exist in current medical practice and in blood transfusion therapy. Blood transfusions are nowadays very safe; however there is still the uncommon risk of infections from blood transfusions. There is also the risk that your baby may have a temporary reaction such as fever, chills, or skin rashes from the blood transfusion.

Risks from the study may include: Giving blood transfusions at too high a hemoglobin level may result not only in more blood transfusions, but the babies may take longer to mature their own bone marrow to produce their own blood. On the other hand, transfusing at too low a hemoglobin could lead to your baby not having enough hemoglobin to carry enough oxygen around the body. We avoid these extremes by transfusing within the ranges of hemoglobin level that doctors nowadays already use.

Should your baby need blood for emergency reasons, your baby will get the blood he/she needs regardless of the study. After the urgent need is over, your baby will return to the study protocol.

Unknown risks and discomforts:
During the entire study, an independent committee will review this study to make sure that it continues to be safe. The researchers will let you know if they learn anything that might make you change your mind about participating in the study.

ARE THERE ANY BENEFITS IF MY BABY PARTICIPATES?

Possible benefits to my baby:
There may be no direct benefit to your baby for taking part in this study. However, your baby may benefit from additional monitoring during the study.

Possible benefits to others or society:
This study will help researchers learn more about the ideal hemoglobin level for the survival and outcome of all premature babies.

WHAT OTHER CHOICES DO I HAVE IF I DON'T WANT TO PARTICIPATE?

If you choose not to participate in this study and if your baby needs a blood transfusion, your baby's doctor will decide at which level of hemoglobin to use in making the decision to transfuse your baby.

CAN RESEARCHERS REMOVE MY BABY FROM THE STUDY?

Researchers may end your baby's participation in this study for a number of reasons, such as if your baby's safety and welfare are at risk. The researchers or the study sponsor might also decide to stop the study at any time.

If you decide to stop your baby from being in the study, or are removed from the study, or the study is stopped, the data collected about your baby up to the point of withdrawal will remain part of the study and may not be removed from the study database.

HOW WILL INFORMATION ABOUT MY BABY AND MY BABY'S PARTICIPATION BE KEPT CONFIDENTIAL?

Researchers will do their best to make sure that your baby's private information is kept confidential. Information about your baby will be handled as confidentially as possible, but participating in research may involve a loss of privacy and the potential for a breach in confidentiality. Study data will be physically and electronically secured. As with any use of electronic means to store data, there is a risk of breach of data security.

Use of personal information that can identify your baby:
All information collected about your baby during the course of this study will be kept confidential to the extent permitted by law.

How information about your baby will be stored:
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 - 26 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. Information that identifies your baby personally will not be released without your written permission.

People and agencies that will have access to your baby's information:
The research team, study sponsor NICHD, data coordinating center at Research Triangle International (RTI), or federal agencies with appropriate regulatory oversight (e.g., Food and Drug Administration (FDA), Office for Human Research Protections (OHRP), Office of Civil Rights (OCR), etc.) may have access to study data and records to monitor the study. Research records provided to authorized, non-UCLA personnel will not contain identifiable information about you. Publications and/or presentations that result from this study will not identify you by name.

How long information from the study will be kept?
Information from the study will be kept for at least 5 years from the conclusion of the study.

ARE THERE ANY COSTS FOR TAKING PART IN THIS STUDY?

You or your insurer will be billed for the costs of any standard medical care you receive during your participation in the study and you will be responsible for any associated co-payments and deductibles. There is a possibility that your medical insurance company may not cover these costs because you are in a research study. If this happens you might have unexpected expenses from being in this study, such as the costs associated with treating side effects. Financial counseling and itemized cost estimates are available upon request.

WILL I BE PAID FOR MY PARTICIPATION?

You will be compensated $100 (in the form of a university check or a gift card) at the time of your baby's 22 - 26 month follow-up visit for your time, parking, and travel expenses. Personal information about you, including your name, address, and social security number, will be released to the UCLA Accounting Office for the purpose of payment.

WHAT OTHER THINGS SHOULD I CONSIDER BEFORE PARTICIPATION?

Researcher Financial Interests in the Study:
The members of the study team have no personal financial interest in the outside entity funding the study or other personal financial interests in entities that might reasonably be affected by the research.

WHO CAN I CONTACT IF I HAVE QUESTIONS ABOUT THE STUDY?

The Research Team:
You may contact Principal Investigators, Meena Garg MD at 310-825-9436 or 310-794-8864 (24 hour voice mail) or Uday Devaskar MD at 310-825-9414 (24 hour voice mail) if you have any questions about this study now or in the future. For after hours, please call the hospital operator at 310-825-6301 and ask them to page Dr. Meena Garg or Dr. Uday Devaskar available 24 hours a day by pager.
In the event of a research related injury or if you experience an adverse reaction, please immediately contact one of the investigators listed above

UCLA Office of the Human Research Protection Program (OHRPP):
If you have questions about your rights while taking part in this study, or you have concerns or suggestions and you want to talk to someone other than the researchers about the study, you may contact the UCLA OHRPP by phone: (310) 825-5344; by email: mirb@research.ucla.edu or U.S. mail: UCLA OHRPP, 11000 Kinross Ave., Suite 211, Box 951694, Los Angeles, CA 90095-1694.

Public Information About this Study:
ClinicalTrials.gov is a website that provides information about federally and privately supported clinical trials. A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time. Information about this study is available on a public registry website (http://clinicaltrials.gov and the identifier number is NCT 01702805).

WHAT HAPPENS IF I BELIEVE MY BABY'S INJURED BECAUSE OF THIS STUDY?
It is important that you promptly tell the researchers if you believe that your baby has been injured because of taking part in this study. You can tell the researcher in person or call the research team at the numbers listed above.

If your baby is injured as a result of being in this study, UCLA will provide necessary medical treatment. The costs of the treatment may be covered by the University of California or the study sponsor NICHD, or billed to you or your insurer just like other medical costs, depending on a number of factors. The University and the study sponsor do not normally provide any other form of compensation for injury. For more information about this, you may call the UCLA Office of the Human Research Protection Program at 310-825-5344 or send an email to mirb@research.ucla.edu.

WHAT ARE MY RIGHTS IF I TAKE PART IN THIS STUDY?
Taking part in this study is your choice. You can choose whether or not you want your baby to participate. Whatever decision you make, there will be no penalty to you and you will not lose any of your regular benefits.

1. You have a right to have all of your questions answered before deciding whether to take part.
2. Your decision will not affect the medical care you receive from UCLA.
3. If you decide to take part, you can leave the study at anytime.
4. If you decide to stop being in this study you should notify the research team right away. The researchers may ask you to complete some procedures in order to protect your safety.
5. If you decide not to take part, you can still get medical care from UCLA.

HOW DO I INDICATE MY AGREEMENT TO PARTICIPATE?
If you agree to participate in this study you should sign and date below. You have been given a copy of this consent form and the Research Participant's Bill of Rights to keep. You will be asked to sign a separate form authorizing access, use, creation, or disclosure of health information about you.

SIGNATURE OF SUBJECT [OR LEGAL REPRESENTATIVE]

_____
Name of Child

_____
Name of Parent or Legal Guardian

_____ _____
Signature of Parent or Legal Guardian Date

SIGNATURE OF PERSON OBTAINING CONSENT
I have explained the research to the subject or his/her parents/guardian and answered all of his/her questions. I believe that he/she understands the information described in this document and freely consents to participate.

_____ _____
Name of Person Obtaining Consent Contact Number

_____ _____
Signature of Person Obtaining Consent Date (must be same as subject's)

_____
Name of Witness

_____ _____
Signature of Witness Date (must be same as subject's)

University of North Carolina at Chapel Hill
Parental Permission for a Minor Child to Participate in a Research Study

Consent Form Version Date: March 25, 2013
IRB Study # 12-2502
Title of Study: 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?
Principal Investigator: Carl L. Bose, MD
Principal Investigator Department: Pediatrics
Principal Investigator Phone number: (919) 966-5063
Principal Investigator Email Address: carl_bose@med.unc.edu
Co-Investigators: Matthew M. Laughon, MD, MPH, Sofia R. Aliaga, MD, MPH, Diane D. Marshall, MD, MPH

Funding Source and/or Sponsor: NIH National Institute Of Child Health And Human Development (NICHD) and National Heart, Lung and Blood Institute (NHLBI)

What are some general things you and you child should know about research studies?
You are being asked to allow your child to take part in a research study. To join the study is voluntary.
You may refuse to give permission, or you may withdraw your permission for your child to be in the study, for any reason, without penalty.

Research studies are designed to obtain new knowledge. This new information may help people in the future. Your child may not receive any direct benefit from being in the research study. There also may be risks to being in research studies. Deciding not to be in the study or leaving the study before it is done will not affect your or your child's relationship with the study doctor, the health care provider, or the University of North Carolina-Chapel Hill. If your child is a patient with an illness, your child does not have to be in the research study in order to receive health care.

Details about this study are discussed below. It is important that you and your child understand this information so that you and your child can make an informed choice about being in this research study.
You will be given a copy of this consent form. You and your child should ask the study doctors named above, or staff members who may assist them, any questions you have about this study at any time.

What is the purpose of this study?
The purpose of this study is to find out when it is best to give blood transfusions to premature babies.

It is not unusual for a premature baby to need a blood transfusion. Blood transfusions are used to treat anemia. Anemia means that there isn't enough hemoglobin in the blood.

Hemoglobin carries oxygen around the body. Premature babies are more prone to anemia for many reasons: their red blood cells have a shorter lifespan than adults; they may not be able to make enough red blood cells to keep up with their growth, and the number of blood samples needed for lab tests.

Doctors can do blood tests to find out if a baby is anemic and may need a blood transfusion. The tests can tell them the amount of hemoglobin in the blood or if there are enough red blood cells (hematocrit test) A low hemoglobin or hematocrit is a sign of anemia. When the hemoglobin or hematocrit falls below a certain level, the baby will need a transfusion. We do not know the best level to use to decide when a baby needs a blood transfusion. Some doctors use a higher level or lower levels of hemoglobin or hematocrit than others to make this decision. This study will help us find out when it is best to transfuse premature babies. Your child is being asked to be in the study because he/she was born before 29 weeks gestation and had a birth weight of 2.2 pounds or less.

In addition to finding when the best hemoglobin or hematocrit level to transfuse babies, we would also like to know if there are any differences in the cost of these treatments. In order to find that out, we will look at billing information for the time that your baby is in the hospital. Billing information will include items and services that the hospital or doctors bill to you or your insurance company.

Are there any reasons your child should not be in this study?

Your child should not be in this study if your baby had a blood transfusion after 6 hours of life or during fetal life, has cyanotic or severe congenital heart disease, hemolytic disease or twin-to twin transfusion syndrome, you are opposed to blood transfusions or you have an inherited blood disorder such as sickle cell disease, thalassemia, hemoglobin C disease.

How many people will take part in this study?

A total of approximately 1824 babies at 18 institutions will take part in this study, including approximately 40 babies from North Carolina Children's Hospital.

How long will your child's part in this study last?

Your baby will remain in the study for approximately 2 years. There will be a follow up appointment scheduled in the Special Infant Care Clinic at 22-26 months adjusted age.

What will happen if your child takes part in the study?

If you agree that your baby should take part in this study, your baby will be randomly assigned (like a flip of a coin) to either the higher level of hemoglobin/hematocrit or the lower level. Both of these levels are in the usual range used by doctors in the Newborn Critical Care Center. The doctor will use this level of hemoglobin/hematocrit to decide when to transfuse the baby. If your baby were to get unexpectedly ill or have an unexpected urgent need for blood transfusion (where everybody would routinely give blood), your baby would get the transfusion regardless of the level of hemoglobin/hematocrit.

All of the blood tests that are done are routine standard of care. We will ask you to complete an economic questionnaire that will help provide us with information as to how families cope with having a baby in the intensive care nursery.

We will arrange for your baby to come back for a 22-26 month follow-up appointment. All extremely premature babies are routinely seen in the Follow-up clinic to check how well they develop and grow.

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.

What are the possible benefits from being in this study?

Research is designed to benefit society by gaining new knowledge. Your child may or may not benefit from being in this study. The benefits to your child from being in this study may be improved developmental outcome at 22-26 months adjusted age if the transfusion threshold to which your baby is assigned is shown to be associated with this improved outcome.

What are the possible risks or discomforts involved from being in this study?

This study will look at whether using a high or low level of hematocrit to transfuse your baby affects your baby's growth and development. We do not know whether using a high or low level would be better for your baby. There are no extra blood tests being done on your baby. All blood tests are done as routine standard of care at your doctor's request. This study does not alter the routine care for your baby. The risks associated with this study are exactly the same risks that exist in current medical practice and in blood transfusion therapy. If your baby needs blood for emergency reasons, where all doctors would routinely give blood, they will get the blood they need. After that urgent need is over, they will then return to the study protocol.

Blood transfusions are generally extremely safe. Blood transfusions given at higher a hemoglobin or hematocrit level may result in more blood transfusions and babies may take longer to mature their own bone marrow to produce their own blood. Blood transfusions given at too low a hemoglobin or hematocrit, could lead to the baby not having enough hemoglobin to carry enough oxygen around the body. However, we avoid these extremes by transfusing within the high or low end of the normal ranges of hemoglobin or hematocrit level that doctors already use.

During the entire study, an independent committee will review this study to make sure that it continues to be safe. There may be uncommon or previously unknown risks. You should report any problems to the study doctor.

If you choose not to give permission for your child to be in the study, what other treatment options do you have?

Your child does not have to be in this research study in order to receive treatment. If you choose not to participate in this study and if your baby needs a blood transfusion, the doctor will decide which hemoglobin or hematocrit level use in making the decision to transfuse your baby.

What if we learn about new findings or information during the study?
You and your child will be given any new information gained during the course of the study that might affect your willingness to continue your child's participation in the study.

How will information about your child be protected?
Participants will not be identified in any report or publication about this study. Although every effort will be made to keep research records private, there may be times when federal or state law requires the disclosure of such records, including personal information. This is very unlikely, but if disclosure is ever required, UNC-Chapel Hill will take steps allowable by law to protect the privacy of personal information. In some cases, your child's information in this research study could be reviewed by representatives of the University, research sponsors, or government agencies (for example, the FDA) for purposes such as quality control or safety.

Information contained in study records is identified with a code rather than your baby's name. Research records are stored in a in a locked office, and are linked to your child through a study number accessible only to UNC-CH neonatal research personnel. Research data forms will be sent via encrypted email or personally delivered to Duke Neonatal Perinatal Research Unit, RTI and/or NICHD. Duke Neonatal Perinatal Research Unit personnel periodically review research charts in the UNC-CH Neonatal research office. A copy of this permission form will go in to your child's medical record. This will allow the doctors caring for your child to know what study drugs or tests your child may be receiving as part of the study and know how to take care of your child if your child has other health problems or needs during the study.

What will happen if your child is injured by this research?
All research involves a chance that something bad might happen. This may include the risk of personal injury. In spite of all safety measures, your child might develop a reaction or injury from being in this study. If such problems occur, the study doctors will help your child get medical care, but any costs for the medical care will be billed to you and/or your insurance company. The University of North Carolina at Chapel Hill has not set aside funds to pay you for any such reactions or injuries, or for the related medical care. However, by signing this form, you and your child do not give up any of your legal rights.

What if you want to stop before your child's part in the study is complete?
You can withdraw your child from this study at any time, without penalty. The investigators also have the right to stop your child's participation at any time. This could be because your child has had an unexpected reaction or because the entire study has been stopped.

Will your child receive anything for being in this study?
Your child will receive a small gift bag, valued at approximately $10-15 dollars, and a $25 gift card at the time of the follow up appointment for taking part in this study. You will be given parking vouchers to cover the cost of parking for the visit.

Will it cost you anything for your child to be in this study?
It will not cost anything extra to be in this study. However, you will be billed for your child's routine medical care. All tests, visits or procedures other than what is done for this study will be related to medical care that is part of the usual care for your child's condition. These would be suggested even if you decided not to allow your child to be in the research study. Here are some examples of routine medical care that may be performed within this study: lab tests, x-rays, ultrasounds, medicine, blood products, doctor's care, IV (intravenous) fluids

Who is sponsoring this study?
This research is funded by National Institute Of Child Health And Human Development (NICHD) and the National Heart, Lung and Blood Institute (NHLBI). This means that the research team is being paid by the sponsor for doing the study. The study doctors do not, however, have a direct financial interest with the sponsor or in the final results of the study.

What if you or your child has questions about this study?
You have the right to ask, and have answered, any questions you may have about this research. If there are questions about the study (including payments), complaints, concerns, or if a research-related injury occurs, contact the study doctors listed on the first page of this form.

A description of this clinical trial will be available on www.clinicaltrials.gov, as required by U.S. Law. The study identifier is NCT 01702805. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

What if there are questions about your child's rights as a research participant?
All research on human volunteers is reviewed by a committee that works to protect your child's rights and welfare. If there are questions or concerns about your child's rights as a research subject, or if you would like to obtain information or offer input, you may contact the Institutional Review Board at 919-966-3113 or by email to IRB_subjects@unc.edu.

Parent's Agreement:

I have read the information provided above about the "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?" research study.

I have asked all the questions I have at this time. I voluntarily give permission to allow my child to participate in this research study.

_____

Printed Name of Research Participant (child)

_____ _____

Signature of Parent Date

_____

Printed Name of Parent

_____ _____

Signature of Research Team Member Obtaining Permission Date

_____

Printed Name of Research Team Member Obtaining Permission

University of North Carolina at Chapel Hill
Parental Permission for a Minor Child to Participate in a Research Study

Consent Form Version Date: 1/28/2013
IRB Study # 12-2502
Title of Study: 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?
Principal Investigator: Carl L. Bose, MD
Principal Investigator Department: Pediatrics
Principal Investigator Phone number: (919) 966-5063
Principal Investigator Email Address: carl_bose@med.unc.edu
Co-Investigators: Matthew M. Laughon, MD, MPH, Sofia R. Aliaga, MD, MPH, Diane D. Marshall, MD, MPH

Funding Source and/or Sponsor: NIH National Institute Of Child Health And Human Development (NICHD) and National Heart, Lung and Blood Institute (NHLBI)

What are some general things you and you child should know about research studies?
You are being asked to allow your child to take part in a research study. To join the study is voluntary.
You may refuse to give permission, or you may withdraw your permission for your child to be in the study, for any reason, without penalty.

Research studies are designed to obtain new knowledge. This new information may help people in the future. Your child may not receive any direct benefit from being in the research study. There also may be risks to being in research studies. Deciding not to be in the study or leaving the study before it is done will not affect your or your child's relationship with the study doctor, the health care provider, or the University of North Carolina-Chapel Hill. If your child is a patient with an illness, your child does not have to be in the research study in order to receive health care.

Details about this study are discussed below. It is important that you and your child understand this information so that you and your child can make an informed choice about being in this research study.
You will be given a copy of this consent form. You and your child should ask the study doctors named above, or staff members who may assist them, any questions you have about this study at any time.

What is the purpose of this study?
The purpose of this study is to find out when it is best to give blood transfusions to premature babies.

It is not unusual for a premature baby to need a blood transfusion. Blood transfusions are used to treat anemia. Anemia means that there isn't enough hemoglobin in the blood.

Hemoglobin carries oxygen around the body. Premature babies are more prone to anemia for many reasons: their red blood cells have a shorter lifespan than adults; they may not be able to make enough red blood cells to keep up with their growth, and the number of blood samples needed for lab tests.

Doctors can do blood tests to find out if a baby is anemic and may need a blood transfusion. The tests can tell them the amount of hemoglobin in the blood or if there are enough red blood cells (hematocrit test) A low hemoglobin or hematocrit is a sign of anemia. When the hemoglobin or hematocrit falls below a certain level, the baby will need a transfusion. We do not know the best level to use to decide when a baby needs a blood transfusion. Some doctors use a higher level or lower levels of hemoglobin or hematocrit than others to make this decision. This study will help us find out when it is best to transfuse premature babies. Your child is being asked to be in the study because he/she was born before 29 weeks gestation and had a birth weight of 2.2 pounds or less.

Are there any reasons your child should not be in this study?

Your child should not be in this study if your baby had a blood transfusion after 6 hours of life or during fetal life, has cyanotic or severe congenital heart disease, hemolytic disease or twin-to twin transfusion syndrome, you are opposed to blood transfusions or you have an inherited blood disorder such as sickle cell disease, thalassemia, hemoglobin C disease.

How many people will take part in this study?

A total of approximately 1824 babies at 18 institutions will take part in this study, including approximately 40 babies from North Carolina Children's Hospital.

How long will your child's part in this study last?

Your baby will remain in the study for approximately 2 years. There will be a follow up appointment scheduled in the Special Infant Care Clinic at 22-26 months adjusted age.

What will happen if your child takes part in the study?

If you agree that your baby should take part in this study, your baby will be randomly assigned (like a flip of a coin) to either the higher level of hemoglobin/hematocrit or the lower level. Both of these levels are in the usual range used by doctors in the Newborn Critical Care Center. The doctor will use this level of hemoglobin/hematocrit to decide when to transfuse the baby. If your baby were to get unexpectedly ill or have an unexpected urgent need for blood transfusion (where everybody would routinely give blood), your baby would get the transfusion regardless of the level of hemoglobin/hematocrit.

All of the blood tests that are done are routine standard of care. We will ask you to complete an economic questionnaire that will help provide us with information as to how families cope with having a baby in the intensive care nursery.

We will arrange for your baby to come back for a 22-26 month follow-up appointment. All extremely premature babies are routinely seen in the Follow-up clinic to check how well they develop and grow.

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.

What are the possible benefits from being in this study?
Research is designed to benefit society by gaining new knowledge. Your child may or may not benefit from being in this study. The benefits to your child from being in this study may be improved developmental outcome at 22-26 months adjusted age if the transfusion threshold to which your baby is assigned is shown to be associated with this improved outcome.

What are the possible risks or discomforts involved from being in this study?
This study will look at whether using a high or low level of hematocrit to transfuse your baby affects your baby's growth and development. We do not know whether using a high or low level would be better for your baby. There are no extra blood tests being done on your baby. All blood tests are done as routine standard of care at your doctor's request. This study does not alter the routine care for your baby. The risks associated with this study are exactly the same risks that exist in current medical practice and in blood transfusion therapy. If your baby needs blood for emergency reasons, where all doctors would routinely give blood, they will get the blood they need. After that urgent need is over, they will then return to the study protocol.

Blood transfusions are generally extremely safe. Blood transfusions given at higher a hemoglobin or hematocrit level may result in more blood transfusions and babies may take longer to mature their own bone marrow to produce their own blood. Blood transfusions given at too low a hemoglobin or hematocrit, could lead to the baby not having enough hemoglobin to carry enough oxygen around the body. However, we avoid these extremes by transfusing within the high or low end of the normal ranges of hemoglobin or hematocrit level that doctors already use.

During the entire study, an independent committee will review this study to make sure that it continues to be safe.

There may be uncommon or previously unknown risks. You should report any problems to the study doctor.

If you choose not to give permission for your child to be in the study, what other treatment options do you have?
Your child does not have to be in this research study in order to receive treatment. If you choose not to participate in this study and if your baby needs a blood transfusion, the doctor will decide which hemoglobin or hematocrit level use in making the decision to transfuse your baby.

What if we learn about new findings or information during the study?
You and your child will be given any new information gained during the course of the study that might affect your willingness to continue your child's participation in the study.

How will information about your child be protected?

Participants will not be identified in any report or publication about this study. Although every effort will be made to keep research records private, there may be times when federal or state law requires the disclosure of such records, including personal information. This is very unlikely, but if disclosure is ever required, UNC-Chapel Hill will take steps allowable by law to protect the privacy of personal information. In some cases, your child's information in this research study could be reviewed by representatives of the University, research sponsors, or government agencies (for example, the FDA) for purposes such as quality control or safety.

Information contained in study records is identified with a code rather than your baby's name. Research records are stored in a in a locked office, and are linked to your child through a study number accessible only to UNC-CH neonatal research personnel. Research data forms will be sent via encrypted email or personally delivered to Duke Neonatal Perinatal Research Unit, RTI and/or NICHD. Duke Neonatal Perinatal Research Unit personnel periodically review research charts in the UNC-CH Neonatal research office. A copy of this permission form will go in to your child's medical record. This will allow the doctors caring for your child to know what study drugs or tests your child may be receiving as part of the study and know how to take care of your child if your child has other health problems or needs during the study.

What will happen if your child is injured by this research?

All research involves a chance that something bad might happen. This may include the risk of personal injury. In spite of all safety measures, your child might develop a reaction or injury from being in this study. If such problems occur, the study doctors will help your child get medical care, but any costs for the medical care will be billed to you and/or your insurance company. The University of North Carolina at Chapel Hill has not set aside funds to pay you for any such reactions or injuries, or for the related medical care. However, by signing this form, you and your child do not give up any of your legal rights.

What if you want to stop before your child's part in the study is complete?

You can withdraw your child from this study at any time, without penalty. The investigators also have the right to stop your child's participation at any time. This could be because your child has had an unexpected reaction or because the entire study has been stopped.

Will your child receive anything for being in this study?

Your child will receive a small gift bag, valued at approximately $10-15 dollars, and a $25 gift card at the time of the follow up appointment for taking part in this study. You will be given parking vouchers to cover the cost of parking for the visit.

Will it cost you anything for your child to be in this study?

It will not cost anything extra to be in this study. However, you will be billed for your child's routine medical care. All tests, visits or procedures other than what is done for this study will be related to medical care that is part of the usual care for your child's condition. These would be suggested even if you decided not to allow your child to be in the research study. Here are some examples of routine medical care that may be performed within this study: lab tests, x-rays, ultrasounds, medicine, blood products, doctor's care, IV (intravenous) fluids

Who is sponsoring this study?
This research is funded by National Institute Of Child Health And Human Development (NICHD) and the National Heart, Lung and Blood Institute (NHLBI). This means that the research team is being paid by the sponsor for doing the study. The study doctors do not, however, have a direct financial interest with the sponsor or in the final results of the study.

What if you or your child has questions about this study?
You have the right to ask, and have answered, any questions you may have about this research. If there are questions about the study (including payments), complaints, concerns, or if a research-related injury occurs, contact the study doctors listed on the first page of this form.

A description of this clinical trial will be available on www.clinicaltrials.gov, as required by U.S. Law. The study identifier is NCT 01702805. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

What if there are questions about your child's rights as a research participant?
All research on human volunteers is reviewed by a committee that works to protect your child's rights and welfare. If there are questions or concerns about your child's rights as a research subject, or if you would like to obtain information or offer input, you may contact the Institutional Review Board at 919-966-3113 or by email to IRB_subjects@unc.edu.

Parent's Agreement:

I have read the information provided above. I have asked all the questions I have at this time. I voluntarily give permission to allow my child to participate in this research study.

_____

Printed Name of Research Participant (child)

_____ _____

Signature of Parent Date

_____

Printed Name of Parent

_____ _____

Signature of Research Team Member Obtaining Permission Date

_____

Printed Name of Research Team Member Obtaining Permission

University of North Carolina at Chapel Hill
Parental Permission for a Minor Child to Participate in a Research Study

Consent Form Version Date: 1/18/2013
IRB Study # 12-2502
Title of Study: 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?
Principal Investigator: Carl L. Bose, MD
Principal Investigator Department: Pediatrics
Principal Investigator Phone number: (919) 966-5063
Principal Investigator Email Address: carl_bose@med.unc.edu
Co-Investigators: Matthew M. Laughon, MD, MPH, Sofia R. Aliaga, MD, MPH, Diane D. Marshall, MD, MPH

Funding Source and/or Sponsor: NIH National Institute Of Child Health And Human Development (NICHD)

What are some general things you and you child should know about research studies?
You are being asked to allow your child to take part in a research study. To join the study is voluntary.
You may refuse to give permission, or you may withdraw your permission for your child to be in the study, for any reason, without penalty.

Research studies are designed to obtain new knowledge. This new information may help people in the future. Your child may not receive any direct benefit from being in the research study. There also may be risks to being in research studies. Deciding not to be in the study or leaving the study before it is done will not affect your or your child's relationship with the study doctor, the health care provider, or the University of North Carolina-Chapel Hill. If your child is a patient with an illness, your child does not have to be in the research study in order to receive health care.

Details about this study are discussed below. It is important that you and your child understand this information so that you and your child can make an informed choice about being in this research study.
You will be given a copy of this consent form. You and your child should ask the study doctors named above, or staff members who may assist them, any questions you have about this study at any time.

What is the purpose of this study?
The purpose of this study is to find out when it is best to give blood transfusions to premature babies.

It is not unusual for a premature baby to need a blood transfusion. Blood transfusions are used to treat anemia. Anemia means that there isn't enough hemoglobin in the blood.

Hemoglobin carries oxygen around the body. Premature babies are more prone to anemia for many reasons: their red blood cells have a shorter lifespan than adults; they may not be able to make enough red blood cells to keep up with their growth, and the number of blood samples needed for lab tests.

Doctors can do blood tests to find out if a baby is anemic and may need a blood transfusion. The tests can tell them the amount of hemoglobin in the blood or if there are enough red blood cells (hematocrit test) A low hemoglobin or hematocrit is a sign of anemia. When the hemoglobin or hematocrit falls below a certain level, the baby will need a transfusion. We do not know the best level to use to decide when a baby needs a blood transfusion. Some doctors use a higher level or lower levels of hemoglobin or hematocrit than others to make this decision. This study will help us find out when it is best to transfuse premature babies. Your child is being asked to be in the study because he/she was born before 29 weeks gestation and had a birth weight of 2.2 pounds or less.

Are there any reasons your child should not be in this study?

Your child should not be in this study if your baby had a blood transfusion after 6 hours of life or during fetal life, has cyanotic or severe congenital heart disease, hemolytic disease or twin-to twin transfusion syndrome, you are opposed to blood transfusions or you have an inherited blood disorder such as sickle cell disease, thalassemia, hemoglobin C disease.

How many people will take part in this study?

A total of approximately 1824 babies at 18 institutions will take part in this study, including approximately 40 babies from North Carolina Children's Hospital.

How long will your child's part in this study last?

Your baby will remain in the study for approximately 2 years. There will be a follow up appointment scheduled in the Special Infant Care Clinic at 22-26 months adjusted age.

What will happen if your child takes part in the study?

If you agree that your baby should take part in this study, your baby will be randomly assigned (like a flip of a coin) to either the higher level of hemoglobin/hematocrit or the lower level. Both of these levels are in the usual range used by doctors in the Newborn Critical Care Center. The doctor will use this level of hemoglobin/hematocrit to decide when to transfuse the baby. If your baby were to get unexpectedly ill or have an unexpected urgent need for blood transfusion (where everybody would routinely give blood), your baby would get the transfusion regardless of the level of hemoglobin/hematocrit.

All of the blood tests that are done are routine standard of care. We will ask you to complete an economic questionnaire that will help provide us with information as to how families cope with having a baby in the intensive care nursery.

We will arrange for your baby to come back for a 22-26 month follow-up appointment. All extremely premature babies are routinely seen in the Follow-up clinic to check how well they develop and grow.

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.

What are the possible benefits from being in this study?
Research is designed to benefit society by gaining new knowledge. Your child may or may not benefit from being in this study. The benefits to your child from being in this study may be improved developmental outcome at 22-26 months adjusted age if the transfusion threshold to which your baby is assigned is shown to be associated with this improved outcome.

What are the possible risks or discomforts involved from being in this study?
This study will look at whether using a high or low level of hematocrit to transufuse your baby affects your baby's growth and development. We do not know whether using a high or low level would be better for your baby. There are no extra blood tests being done on your baby. All blood tests are done as routine standard of care at your doctor's request. This study does not alter the routine care for your baby. The risks associated with this study are exactly the same risks that exist in current medical practice and in blood transfusion therapy. If your baby needs blood for emergency reasons, where all doctors would routinely give blood, they will get the blood they need. After that urgent need is over, they will then return to the study protocol.

Blood transfusions are generally extremely safe. Blood transfusions given at higher a hemoglobin or hematocrit level may result in more blood transfusions and babies may take longer to mature their own bone marrow to produce their own blood. Blood transfusions given at too low a hemoglobin or hematocrit, could lead to the baby not having enough hemoglobin to carry enough oxygen around the body. However, we avoid these extremes by transfusing within the high or low end of the normal ranges of hemoglobin or hematocrit level that doctors already use.

During the entire study, an independent committee will review this study to make sure that it continues to be safe.

There may be uncommon or previously unknown risks. You should report any problems to the study doctor.

If you choose not to give permission for your child to be in the study, what other treatment options do you have?
Your child does not have to be in this research study in order to receive treatment. If you choose not to participate in this study and if your baby needs a blood transfusion, the doctor will decide which hemoglobin or hematocrit level use in making the decision to transfuse your baby.

What if we learn about new findings or information during the study?
You and your child will be given any new information gained during the course of the study that might affect your willingness to continue your child's participation in the study.

How will information about your child be protected?

Participants will not be identified in any report or publication about this study. Although every effort will be made to keep research records private, there may be times when federal or state law requires the disclosure of such records, including personal information. This is very unlikely, but if disclosure is ever required, UNC-Chapel Hill will take steps allowable by law to protect the privacy of personal information. In some cases, your child's information in this research study could be reviewed by representatives of the University, research sponsors, or government agencies (for example, the FDA) for purposes such as quality control or safety.

Information contained in study records is identified with a code rather than your baby's name. Research records are stored in a in a locked office, and are linked to your child through a study number accessible only to UNC-CH neonatal research personnel. Research data forms will be sent via encrypted email or personally delivered to Duke Neonatal Perinatal Research Unit, RTI and/or NICHD. Duke Neonatal Perinatal Research Unit personnel periodically review research charts in the UNC-CH Neonatal research office. A copy of this permission form will go in to your child's medical record. This will allow the doctors caring for your child to know what study drugs or tests your child may be receiving as part of the study and know how to take care of your child if your child has other health problems or needs during the study.

What will happen if your child is injured by this research?

All research involves a chance that something bad might happen. This may include the risk of personal injury. In spite of all safety measures, your child might develop a reaction or injury from being in this study. If such problems occur, the study doctors will help your child get medical care, but any costs for the medical care will be billed to you and/or your insurance company. The University of North Carolina at Chapel Hill has not set aside funds to pay you for any such reactions or injuries, or for the related medical care. However, by signing this form, you and your child do not give up any of your legal rights.

What if you want to stop before your child's part in the study is complete?

You can withdraw your child from this study at any time, without penalty. The investigators also have the right to stop your child's participation at any time. This could be because your child has had an unexpected reaction or because the entire study has been stopped.

Will your child receive anything for being in this study?

Your child will receive a small gift bag, valued at approximately $10-15 dollars, and a $25 gift card at the time of the follow up appointment for taking part in this study. You will be given parking vouchers to cover the cost of parking for the visit.

Will it cost you anything for your child to be in this study?

It will not cost anything extra to be in this study. However, you will be billed for your child's routine medical care. All tests, visits or procedures other than what is done for this study will be related to medical care that is part of the usual care for your child's condition. These would be suggested even if you decided not to allow your child to be in the research study. Here are some examples of routine medical care that may be performed within this study: lab tests, x-rays, ultrasounds, medicine, blood products, doctor's care, IV (intravenous) fluids

Who is sponsoring this study?
This research is funded by National Institute Of Child Health And Human Development (NICHD). This means that the research team is being paid by the sponsor for doing the study. The study doctors do not, however, have a direct financial interest with the sponsor or in the final results of the study.

What if you or your child has questions about this study?
You have the right to ask, and have answered, any questions you may have about this research. If there are questions about the study (including payments), complaints, concerns, or if a research-related injury occurs, contact the study doctors listed on the first page of this form.

A description of this clinical trial will be available on www.clinicaltrials.gov, as required by U.S. Law. The study identifier is NCT 01702805. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

What if there are questions about your child's rights as a research participant?
All research on human volunteers is reviewed by a committee that works to protect your child's rights and welfare. If there are questions or concerns about your child's rights as a research subject, or if you would like to obtain information or offer input, you may contact the Institutional Review Board at 919-966-3113 or by email to IRB_subjects@unc.edu.

Parent's Agreement:

I have read the information provided above. I have asked all the questions I have at this time. I voluntarily give permission to allow my child to participate in this research study.

_____

Printed Name of Research Participant (child)

_____ _____

Signature of Parent Date

_____

Printed Name of Parent

_____ _____

Signature of Research Team Member Obtaining Permission Date

_____

Printed Name of Research Team Member Obtaining Permission

Parental Permission/Research Informed Consent

Title of Study: 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?

Principal Investigator (PI): Beena Sood, MD MS
Children's Hospital of Michigan
3901 Beaubien, #4C19
Detroit, MI 48201
313-745-5638

Funding source: *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD)

National Heart Lung and Blood Institute (NHLBI)

Purpose

You are being asked to allow your child to be in a research study because he/she was born prematurely and of low birth weight (≤1000 grams which is less than about 2.2 pounds). This research study is being done to better understand when premature infants should receive a blood transfusion of red blood cells. This study is being conducted at Hutzel Women's Hospital and Children's Hospital of Michigan here at Wayne State University and at seventeen other university medical centers across the United States through the NICHD sponsored Neonatal Research Network. The estimated number of study participants to be enrolled at Wayne State University is about 150 as well as about 1674 throughout other parts of the country for a total of 1824 participants. **Please read this form and ask any questions you may have before agreeing to be in the study.**

Babies born prematurely are at a higher risk for many problems than babies born at full term. Because premature babies need intensive care, they need a lot of blood tests to monitor their care. Blood contains red cells, which carry a molecule called hemoglobin. Hemoglobin is essential for life as it carries oxygen around the body. Premature infants cannot make red blood cells easily and so become anemic and often require blood transfusion. About 90% of premature babies receive at least one blood transfusion during their stay in the NICU.

Anemia is measured by the level of hemoglobin in the blood. Hemoglobin levels are used by doctors as a measure of how many red blood cells are circulating in the body. When the hemoglobin falls below a certain level is when babies are given blood transfusions. However, some doctors tend to use a higher level of hemoglobin and some doctors tend to use a lower level of hemoglobin. The reason doctors use different levels is that we don't know which level of hemoglobin is better.

Premature babies are also at a higher risk of problems with growth and development. Transfusions at different hemoglobin levels and developmental outcome are being examined. This study aims to help find out when it is best to transfuse babies.

Study Procedures

If you agree for your child to take part in this research study, he/she will be randomly assigned to either the higher level of hemoglobin or the lower level. Your child will have an equal chance of being assigned to either level. The doctors will use this level of hemoglobin to decide when your child is to receive a blood transfusion. Both of these levels are in the usual range used by doctors in the NICU.

Premature babies sometimes get unexpectedly ill or have an unexpected urgent need for blood transfusion, where every doctor would routinely give blood. If this were to happen with your child, he/she would get the transfusion regardless of the level of hemoglobin.

To follow your child's growth, weekly measurements of head circumference will be done. We will collect information from your child's medical record, including information about hemoglobin levels, any transfusions given, ventilator (breathing machine) and oxygen requirements. Your child's care will otherwise continue as per standard clinical care in the nursery.

There will be no blood drawn for this study. All blood tests your child has in the NICU will be ordered by your child's doctor as routine standard of care.

We will ask you to complete a questionnaire that will help provide us with information as to how families may be affected economically by having a baby in the NICU.

When your child is about two years old, (22-26 months from his/her "due date"), your child will be seen at Children's Hospital of Michigan for an evaluation of his/her growth and development. During this 2-3 hour follow-up visit, you will be asked questions about how your child is doing (approximately 30 minutes) and a pediatrician will examine your child (approximately 30 minutes). Your child will undergo developmental testing by a trained psychologist or tester (lasting 1-2 hours). Following the clinic visit, a letter summarizing the visit findings will be sent to your child's doctor if you request. In order to contact you following your child's hospital stay, we will ask for your contact information including home address, home and cell phone numbers, email address, and your permission to use public internet search pages in case we are unable to contact you. This visit is the end point of the study; we would however like your permission to continue to keep in contact with you and your child beyond this time in case the study analysis shows a need or an opportunity for additional follow-up.

Benefits

There may be no direct benefit for your child from participating in this study. However, your child may benefit from additional monitoring during the study. It is hoped that information from this study may help in the treatment of babies born prematurely now or in the future.

Risks

There are no known risks at this time to participation in this study.

There are no additional risks to those that exist in current medical practice and in blood transfusion therapy which is in general extremely safe. The levels of hemoglobin used for transfusions in this study are within the ranges currently used by doctors as standard of care in the NICU.

If your child should have an unexpected urgent need for a blood transfusion, where doctors would give blood, your child would get the blood they need regardless of the level of hemoglobin. After that urgent need is over, your child will then return to the study assigned hemoglobin level.

There may also be risks involved from taking part in this study that are not known to researchers at this time.

Alternatives
You have the choice to not allow your child to take part in this study. If you choose not to participate in this study and if your baby needs a blood transfusion, the doctor will decide at which level of hemoglobin to use in making the decision to transfuse your baby.

Study Costs
Participation in this study will be of no cost to you. Transportation, if needed, will be provided at the time of the follow-up visit. All examinations, procedures and tests done solely for the purposes of this study will be provided free of cost to you. The costs of your regular treatment, which is not directly associated with this study, will be your responsibility or the responsibility of your health insurance company.

Compensation
At the time of the 22-26 month follow-up visit, you will be compensated $50 (in the form of gift certificates) for your time and expenses of travel. In addition, your child may receive a book or small toy at the time of the visit.

Research Related Injuries
In the event that this research related activity results in an injury, treatment will be made available including first aid, emergency treatment, and follow-up care as needed. Care for such will be billed in the ordinary manner to you or your insurance company. No reimbursement, compensation, or free medical care is offered by Hutzel Women's Hospital, Children's Hospital of Michigan, Wayne State University, or the sponsors of this study NICHD and NHLBI. If you think that your child has suffered a research related injury, contact the PI right away at (313) 745-5638.

Confidentiality
All information collected about your child during the course of this study will be kept confidential to the extent permitted by law. Your child will be identified in the research records by a code name or number. Information that identifies your child personally will not be released without your written permission. However, the study sponsor, the Institutional Review Board (IRB) at Wayne State University, or federal agencies with appropriate regulatory oversight [e.g., Food and Drug Administration (FDA), Office for Human Research Protections (OHRP), Office of Civil Rights (OCR), etc.) may review your records.
When the results of this research are published or discussed in conferences, no information will be included that would reveal your child's identity.

A description of this clinical trial, record number NCT # 01702805, is registered and will be available on http://ClinicalTrials.gov as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Voluntary Participation/Withdrawal

Taking part in this study is voluntary. You have the right to choose not to allow your child to take part in this study. If you decide to allow your child to take part in the study you can later change your mind and withdraw from the study. You are free to only answer questions that you want to answer. You are free to withdraw your child from participation in this study at any time. Your decisions will not change any present or future relationship with Wayne State University or its affiliates, or other services you or your child are entitled to receive.

The PI may stop your child's participation in this study without your consent. If your child has any side effects that are very serious or if your child becomes ill during the course of the research study your child may have to drop out, even if you would like to continue. The PI will make the decision and let you know if it is not possible for your child to continue. The decision that is made is to protect your child's health and safety, or because it is part of the research plan that people who develop certain conditions or do not follow the instructions from the study doctor may not continue to participate.

While taking part in this study you will be told of any important new findings that may change your willingness to continue to take part in the research.

Questions

If you have any questions about this study now or in the future, you may contact Dr. Beena Sood or one of her research team members at the following phone number (313) 745-5638. If you have questions or concerns about you or your child's rights as a research participant, the Chair of the Institutional Review Board can be contacted at (313) 577-1628. If you are unable to contact the research staff, or if you want to talk to someone other than the research staff, you may also call (313) 577-1628 to ask questions or voice concerns or complaints.

Consent to Participate in a Research Study:

To voluntarily agree to have your child take part in this study, you must sign on the line below. If you choose to have your child take part in this study, you may withdraw them at any time. You are not giving up any of your or your child's legal rights by signing this form. Your signature below indicates that you have read, or had read to you, this entire consent form, including the risks and benefits, and have had all of your questions answered. You will be given a copy of this consent form.

Name of Participant	Date of Birth
Signature of Parent/ Legally Authorized Guardian	Date
Printed Name of Parent Authorized Guardian	Time
*Signature of Parent/ Legally Authorized Guardian	Date
*Printed Name of Parent Authorized Guardian	Time
**Signature of Witness (When applicable)	Date
Printed Name of Witness	Time
Signature of Person Obtaining Consent	Date
Printed Name of Person Obtaining Consent	Time
Signature of translator	Date
Printed name of translator	Time

* Both parent's signatures should be obtained however both are **required** for level 3 studies

** Use when parent/guardian has had consent form read to them (i.e., illiterate, legally blind, translated into foreign language).

Continue to HIPAA Authorization on next page

APPROVAL PERIOD
MAR 22 '13 FEB 13 '14
WAYNE STATE UNIVERSITY INSTITUTIONAL REVIEW BOARD

HIPAA Authorization

A federal regulation, known as the "Health Insurance Portability and Accountability Act (HIPAA)" gives you certain rights concerning the use and disclosure (sharing with others) of your Protected Health Information (PHI). This regulation provides safeguards for the privacy and security of your information. Your permission (authorization) is required for the use and sharing of any protected health information collected as part of this research study. If you are not willing to sign this authorization to use and/or disclose your PHI by the research team, you will not be eligible to take part in this research study.

The principal investigator (PI) and her research team will use your medical records and information created or collected as part of this research study. Your PHI is important for the PI and her research team in order to collect information about you during the study, to be able to contact you if needed, and to provide treatments to you during the study, if required. The PI may send out your study related health information to the sponsor or other entities involved in this study.

Your medical records, which may contain information that directly identifies you, may be reviewed by representatives from groups identified below. The purpose of these reviews is to assure the study is being conducted properly, that data is being obtained correctly or for other uses authorized by law. These reviews occur at the study site or in the PI's research office and can take place anytime during the study or after the study has ended.

The PHI that will be "USED" for this research includes the following: name, address (street address, city, state and zip code), e-mail address, elements of dates, telephone numbers, fax numbers, medical record number and any unique identifying numbers or characteristics or code.

The PHI that will be "DISCLOSED" or shared with others for this research includes the following: elements of dates and any unique identifying numbers or characteristics or code.

Your study information may be **used** or **shared** with the following people or groups:

- The PI, co-investigators, and key personnel of WSU associated with the research project
- WSU's Institutional Review Boards (IRB)
- Authorized members of WSU's workforce who may need to access your information in the performance of their duties.
- The study Sponsors NICHD, NHLBI or representative, including companies it hires to provide study related services, which include: the study data coordinating center Research Triangle International (RTI)
- Federal agencies with appropriate regulatory oversight (e.g., FDA, OHRP, OCR, etc.) may review your records.

Once your information has been released according to this Authorization, it could be released again and may no longer be protected by the HIPAA regulations.

This Authorization does not expire. The research team may need to correct it or provide missing information about you even after the study has ended, and your medical records may be needed to assist in this process.

During your participation in this study you will have access to your medical record and any study information that is part of that record. The PI is not required to release research information that is not part of your medical record.

You may withdraw (take back) your permission for the **use** and **disclosure** of your PHI for this research at anytime, by **writing** to the PI at the address on the first page of this form. Even if you withdraw your permission, the PI for the research project may still use your PHI that was collected prior to your written request if that information is necessary to the study. If you withdraw your permission for use of your PHI, you will also be withdrawn from the research project. Withdrawing your authorization **will not** affect the health care that will be provided by the Detroit Medical Center and/or the WSU School of Medicine Practice Plans.

Authorization to use and disclose PHI

- By signing this document, you are authorizing the PI to **use** and **disclose** PHI collected about you for the research purposes as described above.

_____ _____

Signature of participant Date

_____

Printed name of participant

- For participants unable to give Authorization, the following individual is acting on behalf of the research participant (e.g., children, mentally impaired, etc.).

_____ _____

Signature of authorized representative Date

_____ _____

Printed name of authorized representative Relationship to the participant

_____ _____

Signature of person obtaining Authorization Date

_____

Printed name of person obtaining Authorization