# Phase 1 Trial of Bevacizumab Treatment for Severe Retinopathy of Prematurity

## Informed Consent Form

April 13, 2018

NCT02390531

**RETINOPATHY OF PREMATURITY 1 (ROP1)**
**Phase 1 Trial of Bevacizumab Treatment for Severe Retinopathy of Prematurity**
**(Protocol Version 3.1)**
**Template Informed Consent Form**

## 1. Introduction

We are asking you to consider having your infant take part in a research study. The study is being conducted by the Pediatric Eye Disease Investigator Group. Your infant's eye doctor is a member of this group. The Jaeb Center for Health Research in Tampa, FL is the coordinating center which is organizing the study. The National Eye Institute is paying for the study. The institute is part of the federal government. This form is part of the process to inform you about the research study. Research is a scientific way to learn about medical conditions and/or treatments.

First, we want you to know that participation is voluntary. Refusal to participate will involve no penalty or loss of benefits to which your infant is otherwise entitled. Also, you may stop your infant's participation at any time without penalty or loss of benefits to which your infant is otherwise entitled. Before you decide whether to have your infant take part in the study, please take as much time as you need to ask any questions. You may discuss this study with your infant's doctors, the medical staff, family, and/or friends. For your infant to be in the study, you will need to sign this form.

## 2. Information about the Study

Your infant has a condition called retinopathy of prematurity (ROP), which is a disease in which the blood vessels inside the eye do not grow the way they should. ROP can occur when an infant is born too early. In some cases, ROP may lead to vision loss or blindness. Your infant's ROP is bad enough that it needs to be treated, and treatment will lower the chance that vision loss will occur.

There are different ways to treat ROP. It is often treated using a laser. The laser stops the blood vessels from growing the wrong way and usually prevents vision loss. Until recently, laser was used for almost all cases of severe ROP. A newer way to treat severe ROP is with a drug called bevacizumab, commonly known as Avastin® (Genentech, South San Francisco, CA). It is the same drug that is used to treat some eye diseases in adults, and, in much higher doses, some cancers in adults. Avastin is injected into the eye with a fine needle, and it works by stopping the blood vessels from growing the wrong way. In some cases, Avastin seems to work even better than laser. However, for some infants, it is possible that it does not work better than laser, or that it does not work as well.

Avastin has been used for several years to treat ROP, but it has not been approved by the United States Food and Drug Administration (FDA) for this purpose. Therefore, it is considered an experimental drug when used to treat ROP. Avastin appears to treat ROP well and to be safe. Some Avastin gets into the blood when it is injected into the eye. It is possible that this could cause some side effects in the body, such as affecting how organs develop. Injecting a lower amount of Avastin into the eye may be safer for an infant, but it is not known how little Avastin can be injected and still treat the ROP. The purpose of this study is to find a lower amount of Avastin that treats ROP well.

In this study, 10-14 infants will receive a low dose of Avastin in one eye, which is about one-half of the dose that is most commonly used. If that dose works well, then one-half of that dose will be used for another 10-14 infants. An expert committee will review the results before approving the testing of each lower dose. Up to 9 doses (the starting dose plus 8 lower doses, each one-half of the previous dose) will be used in this study.

You are being asked to have your infant take part in the study because he/she has severe ROP that needs treatment. The study will include up to 201 infants with ROP at pediatric hospitals throughout North

America. Your infant would be in the study for one year after your original due date.

**3. Study Procedures**

If your infant is in the study, he/she will have one injection of Avastin into one or both eyes. If both of your infant's eyes need treatment for ROP, a computer program will be used to decide which eye will receive the study dose of Avastin. This is like flipping a coin. If only one of your infant's eyes needs treatment, then that eye will receive the study dose of Avastin. The study dose of Avastin is the amount of medication that is currently being tested in the study. You and your infant's doctor will not be told this amount. If both eyes need treatment, then your infant's eye doctor may choose to treat the other eye with laser or with the last dose that worked well in the study.

*Injection of Avastin*

The injection into the eye will be performed by an ophthalmologist (eye surgeon) and will be done through a small needle after your infant receives anesthesia (numbing) to the area of the injection.

Your infant may require sedation in accordance with your neonatologist's usual routine.

*Amount of Avastin*

The lowest amount of Avastin needed to treat ROP is not known. The purpose of this study is to find out a lower amount of Avastin that works well for ROP. The amount of Avastin used in this study will start at about half the amount that is commonly used to treat ROP. This lower amount is used by some doctors and has worked well. The amount of Avastin will continue to be lowered as long as it works well for at least 8 of 10 infants who receive each amount. Also, an expert committee will review the results from each dose before approving the testing of a lower dose. If the lower amount of Avastin does not work well for your infant, then your doctor may use another treatment as soon as 3 days after the injection of Avastin.

Your infant will only receive one study injection of Avastin as part of this protocol. The amount of Avastin your infant receives will depend on how other infants in the study have responded to treatment. You and your doctor will not be told the amount and will not be able to choose the amount of Avastin that your infant receives. If this is unacceptable to you, you should not enroll your infant in the study.

Any additional Avastin injections would be for treatment purposes at the discretion of your eye doctor and not part of the study protocol. However, information about your child's response to any additional injections will be gathered.

Follow-up Visits

After the injection, your infant's eye doctor will examine your infant the next day, and if needed, 3 to 5 days after that. Your infant will be examined at least once each week for 4 weeks after the injection. Your infant's eye doctor may decide that more examinations are needed for your infant, just as if your infant were not part of this study. If your infant's eyes do not respond to the Avastin, then your infant's doctor may choose to use additional treatment, such as a higher dose of Avastin or laser. Your infant's eye doctor will decide which type of additional treatment would be best for your infant.

At each exam, the eye doctor will check your infant's eyes to make sure that the ROP has responded to treatment. It is possible that ROP can seem to get better but then come back, even several weeks after

treatment. At each exam, the eye doctor will also check to make sure the rest of your infant's eye is healthy.

After the 4 week exam, your infant will have a study visit 12 months after your original due date. Additional examinations between 4 weeks and 12 months will be as per usual care of your infant's eye doctor. You may contact your doctor at any time to report any problems your infant is having.

Six months after your original due date we will collect information from eye exams that your child received since the 4-week visit. We will collect this information again at the 12-month visit. You may be asked to sign a medical records release form if he/she has been followed by another physician.

**4. Risks**

Risks of Injection

The risks of injection are the same whether your infant receives Avastin as part of a study or not. There is a very small chance that the drugs used to numb the eye before the injection could cause an allergic reaction. Some bleeding on the white of the eye at the place where the needle enters the eye may occur. There may be some mild discomfort, tearing, and itching that may last a few days. Right after the injection, the pressure in the eye may go up, but this usually goes away on its own. Rarely this increase in pressure needs to be treated with eye drops or by removing some of the fluid within the eye. It is very unlikely, but possible, that the Avastin injection will cause or lead to bleeding inside the eye, cataract, retinal detachment, need for additional surgery, blindness, or loss of the eye. However, these complications could also occur after laser treatment or as a result of severe ROP. A rare complication of injection is infection inside the eye, which may cause loss of vision. Infections inside the eye are treated with antibiotics injected into the eye. While preparing your child for the injection, your infant's heart or breathing rate could slow. This might decrease their blood oxygen level. This also could happen during the injection or after the injection. In almost all cases, these effects are temporary and cause no permanent harm. But permanent damage to the brain or other organs could happen in rare cases. Death is even possible although not expected to occur related to an injection in any infant in the study.

Risks of Avastin

Tests have shown that low levels of Avastin can reach an infant's blood after injection into the eye. It is unknown how much Avastin leaves the eye or its risk of side effects in the body. Less Avastin injected into the eye may lead to less Avastin leaving the eye, which may lower the risk of problems. Doctors do not think it is likely that the amount of Avastin leaving the eye will have any harmful side effects to an infant's organs as they develop, but the risk is unknown. We want to minimize this risk by giving a smaller amount of Avastin that works well, which is why this study is being done. Your infant will be watched for side effects. Examples of possible side effects involving the body are slowed healing or more bleeding of a wound.

Risks for Infants with ROP in Both Eyes

Infants with ROP in both eyes will have Avastin treatment in one eye and laser or Avastin treatment in the other eye. Eyes treated with laser may end up being more nearsighted than the eye that is treated with Avastin.

Risks of Eye Examinations

The risks and discomforts of the eye examinations are the same whether or not your infant takes part in

the study. There may be some redness or, rarely, bleeding on the surface of the eye after the eye is examined. Some infants have a drop in the blood oxygen level or a slowing of the heart rate during or after the eye exams.

Unknown Risks

Although we have tried to list all possible risks and discomforts with this study, there may be others that we do not know about at this time. These unknown risks of the treatment would be the same whether your infant was receiving Avastin as part of this study or not.

**5. Benefits of Participation**

Your infant needs treatment for ROP. As part of the study, your infant will receive treatment. Your infant's ROP is likely to improve during the study, but it is possible that it will not improve and could worsen. Your infant may not directly benefit from taking part in the study. However, the information will help doctors treat infants with ROP in the future.

**6. Alternative Procedures or Treatment**

The alternative to taking part in the study is to not take part. Your infant does not have to be in this study in order to get treatment for severe ROP.

**7. Other Considerations**

We will send the information about your infant's eyes to a central computer. The computer is located at the Jaeb Center for Health Research in Tampa, Florida.

In addition, the Jaeb Center for Health Research in Tampa will be provided with information on how to contact you. This contact information will be kept separate from your infant's research data.

- During the study, you may receive calls from the coordinating center to help schedule an office visit for your child. If we are not able to reach you when we try to schedule your child's follow-up visit, we will try to contact you through the other information you have given us. If this is not successful, we may use the information you have given us to try to locate you through the use of a third-party search service.
- You will be given a toll-free number (888-797-3344) to call the coordinating center any time you have questions.
- You will also receive updates and information about the study in the mail.

We will report the results of the study in medical journals and at scientific meetings. We will not identify any of the infants who take part in the study. In addition, after the study is completed, a dataset will be made available to the public that will not include any information that might identify your infant. Your infant's records will be confidential.

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 your infant. At most, the Web site will include a summary of the results. You can search this Web site at any time.

**8. Costs**

- The National Eye Institute will provide funds for services specific to the research study. It will not cover patient services considered to be usual patient care.
- All exams in this study are considered to be part of usual care. These exams would be needed whether

your infant was in the study or not. The costs of the exams will be your or your insurance company's responsibility.

- The cost of the Avastin itself will be covered by the study.
- You or your insurance company will be responsible for the cost of procedures, complications, or additional treatment, since treatment for ROP is needed whether or not your infant is in the study.

**9. Compensation**

You will be given a $50 debit card for completion of the 12-month visit required by the study after your infant has been released from the hospital. This is meant to cover your time involved in the study and any travel expenses involved. If your expenses are more than $50 and you will be unable to complete the study visit without additional funds, you may discuss this with the study staff, and additional funds may be available to pay for your costs.

**10. Research-Related Injuries**

Medical care is available if your infant has a research-related injury. If your infant has an emergency, your infant can get emergency care. If possible, you should tell the emergency care medical staff that your infant is in a research study. You should also tell your infant's eye doctor about the emergency as soon as possible.

The costs of care will be your or your insurance company's responsibility. The study will not pay for lost wages or for direct or indirect losses. The ***[name of institution]*** will not pay for medical expenses or any other expenses for injuries related to the research. You can get more information about research-related injuries from the Office of the Institutional Review Board [***phone number***].

You can get more information about research-related injuries from your infant's eye doctor (see contact information on the last page) or from the coordinating center staff at the Jaeb Center (toll-free at 888-797-3344).

**11. Withdrawal from the Study**

It is up to you whether your infant takes part in this study. You can withdraw your infant from the study at any time by contacting your infant's eye doctor and by letting him/her know in writing that you are withdrawing your infant (see contact information on the last page).

You will be told of any relevant new scientific findings during the study. These findings might affect your willingness to have your infant continue in this study.

Your infant's doctor or individuals in charge of this study may stop your infant's participation in the study. Some possible reasons for this include:

- Your doctor decides that continued participation would be harmful to your infant.
- The study is stopped.
- There are unanticipated circumstances.

If your infant leaves the study early, the study will still use the data which were already collected.

If you have any questions about the study at any time, you should speak with Dr. [***name of investigator]*** or one of his/her staff ***[phone number]***. If you have questions about your infant's rights as a research subject, you should contact the Institutional Review Board administrator ***[name and phone number]***. You may also call the coordinating center staff toll-free at 888-797-3344 should you have any questions at any time.

**12. How will my child's information be protected and kept confidential?**

***Note: ~customize sections A- E for your IRB here or as separate document per IRB requirements~***
***Below is Jaeb Center for Health Research IRB's HIPAA language for ICF as an example for you:***

As required by law, study related records with identifying information will be kept confidential. Safeguards for authorized access, security, and privacy of your child's information have been put in place by the Federal Privacy Regulations. Unless the law requires it, your child's name, address, social security number, telephone number, or any other direct identifying information will not be used to identify you or your child.

**A. Purpose of Authorization**
We have rules to protect information about your child. Federal and state laws and the federal medical Privacy Rule also protect your child's information. By signing this form you provide your permission, called your "authorization," for the use and disclosure of information protected by the Privacy Rule.

You must sign the **Protected Health Information Authorization** at the end of this form if you want your child to be in the study. When you sign the form, you give permission for the use and disclosure of your child's Protected Health Information (PHI) for the study. PHI is health information that identifies your child for this study. Your authorization is beneficial and important for the study. Without your authorization, your child will not be able to be in it.

**B. Use and Disclosure of the PHI**
Your child's study doctor will collect information about your child. This information includes things learned from procedures listed and described in this form as well as his or her name, address, date of birth, and information from medical records. Your child's name, address, telephone number, and social security number are examples of identifiable information.

A code number will go with the study results instead of your child's name, address, telephone number, or social security number. Your child's study results will be given to the Jaeb Center for Health Research. The Jaeb Center is the coordinating center for the study. It is located in Tampa, Florida.

This doctor's office will not disclose study results that have identifiable information except as explained in Section C. or when required by law. The Jaeb Center and this doctor's office will guard the privacy of your child's study PHI.

Study results without the protected information may appear in medical journals and be shared at scientific meetings. Your child's records will be confidential. No one will disclose the identity of your child in a medical journal or at a scientific meeting.

**C. Authorized Recipients and Users**
People outside of this doctor's office and the Jaeb Center may need to see or receive your child's information for this study. Some examples include: government agencies (such as the Food and

Drug Administration), safety monitors, other sites in the study, and companies that sponsor the study.

In most cases the information will have a code number with it instead of your child's name, address, telephone number, or social security number.

There are some situations where the information will not have a code number with it. If so, people outside this doctor's office who assist in your child's care may see your child's study PHI. They may not be covered by the federal Privacy Rule. We try to make sure that everyone who needs to see your child's information keeps it confidential – but we cannot guarantee that your child's information will not be disclosed.

**D. Cancellation of Authorization**

Over the course of the study, you will be told of any new scientific findings that might affect your willingness to have your child stay in this study.

You may cancel your permission for the use and disclosure of your child's study PHI at any time. You need to contact your child's study doctor and give him/her a notice of cancellation in writing. When you cancel your permission or when you withdraw your child from the study directly, your child is no longer part of the study. No new information about your child will be gathered for the study except when it is on an adverse (unfavorable) event that is related or potentially related to the study. If one happens, your child's entire medical record may need to be reviewed.

**E. 50 Year Expiration Date and Indefinite Expiration Date**

Some of your child's study PHI does not have a code number with it. Your permission for the use and disclosure of this PHI lasts 50 years from the date of your signature or until the end of the study, whichever is sooner.

The rest of your child's study PHI does have a code number with it. When it is collected, it becomes a research report. Your permission for the use and disclosure of these coded data will never end. These coded data do not have your child's name, address, telephone number, or social security number. *The above supports the HIPAA Privacy Rule – 45 CFR 164.508*

**Subject's Name** *printed* _____

**Description of Representative's Authority to Act for the Subject**_____

**Protected Health Information Authorization**

***By signing, you authorize the use and disclosure of your (infant's) protected health information. This information is collected as part of your (infant's) participation in this study.***

_____ _____
Signature Date

**Study Enrollment**

***By signing, you agree to (have your infant) take part in this study. Your signature means that:***

- ***you have read this informed consent form about the study named below;***
- ***you have been given the chance to discuss the study and to ask questions;***
- ***you have verbally summarized your understanding of the study to the person who is explaining it to you; and***
- ***you freely choose to (have your infant) participate.***

**Name of Study:** Phase 1 Trial of Bevacizumab Treatment for Severe Retinopathy of Prematurity

_____ _____
Signature Date

***I certify that to the best of my knowledge the subject (parent/guardian) understands the nature, demands, risks, and benefits involved in his/her (infant's) participation in this study.***

_____ _____
Investigator's Signature Date

**You will be given a signed copy of this document in case you want to read it again.**

**Investigator Contact Information**

**Name of Investigators:** [*list all investigators at site*]

_____
_____
_____
_____

**Address:** _____
_____

**Telephone:** _____