INDIANA UNIVERSITY INFORMED CONSENT STATEMENT FOR

STUDY TITLE: Natural Berry Extract Therapy for Hemangiomas

PRINCIPAL INVESTIGATOR: Gayle Gordillo, MD

CONTACT TELEPHONE NUMBER: 317-944-5283 (24 hours a day, 7 days a week)

NOTE: The words "your child" are used in this consent form. These words refer to the study volunteer.

1) INTRODUCTION

We invite your child to be in this research study. Using this form as a guide, we will explain the study to you. If you have any questions about the study, please ask. By signing this form, you agree to allow your child to be in this study. If you do not want your child to be in this study, all regular and standard medical care will still be available to your child here at Indiana University. Participation is voluntary. Your child can leave this study at any time.

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

2) WHY ARE WE DOING THIS RESEARCH STUDY?

This is a study to find out ***if giving children powdered berries can make their hemangiomas (birthmarks) shrink.*** There are other medications available to make hemangiomas shrink, but they all have serious side effects. As a result of these risks, many children do not get treatment to make their hemangiomas get better. In previous work done by this group of investigators using mice, the berry therapy has been shown to shrink hemangiomas. This same group of investigators also found that children with hemangiomas that are actively getting bigger will have a small piece of genetic material called microRNA 126 present in their urine at levels much higher levels than healthy children without hemangiomas. When the hemangioma stops growing, the microRNA 126 level decreases to same levels observed in children without hemangiomas. The goal of this study is to see if berry therapy can make hemangiomas shrink and also see if it can make microRNA 126 levels in urine decrease to levels seen in children without hemangiomas.

The berry therapy product, PediaBerry™, has not been approved by the Food and Drug Administration and its use to treat hemangiomas is considered experimental. The individual berry powders found in PediaBerry™ and the cream that is mixed with the PediaBerry™ are all organic and produced using good manufacturing processes that are approved by the Food and Drug Administration.

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

If you agree to allow your child to participate, your child will be one of up to 66 subjects from two sites will who participate in this study. Up to 16 subjects are expected to participate from this site.

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

During this study, we will compare PediaBerry™ to a placebo. A placebo is made to look like PediaBerry™, but it will contain no active medicine. You will not know whether you are taking the study medicine or the placebo.

This study is randomized. Randomized means that each subject will be picked by chance, like tossing a coin or drawing straws, to receive the study medicine or placebo. Each subject has a 2 out of 3 chance of receiving study medicine and a 1 out of 3 chance of receiving placebo.

This study is blinded. Blinded means that the study team and you will not know who is receiving PediaBerry™ or placebo. In case of a medical emergency, there is a way for the study team to quickly find out what each subject is receiving.

To test whether berry therapy can shrink hemangiomas, some subjects will be given berry powder and some subjects will be given a placebo, which is a powder that looks like the berry therapy but doesn't have any berry products in it. The powdered berries or placebo will come in a single use foil packet and will be mixed with a cream that will be applied directly to the hemangioma. A separate foil package of berry powder/placebo will be opened and mixed with water and some of solution given by mouth. Both the topical study medication and oral study medication will be administered daily, and each will be prepared fresh daily. The study staff or video recording will show you exactly how to prepare the cream and the solution and how much to give your child. The amount of cream and solution is based on the weight of your child. The study staff will also provide all the cream and powder and the dropper for giving berry therapy by mouth and a small syringe to collect the right volume of cream to be applied to the hemangioma. If your child has several hemangiomas, the cream will only be applied to the largest one. The staff will give you a clear plastic dressing to place over the cream to keep it on the hemangioma. The dressing may be removed and the Pediaberry contents wiped off immediately prior to bathing. The dressing can be moistened with water to loosen it before removal. Please wait at least five (5) hours after Pediaberry application before giving your child a bath. Your child will receive berry/placebo therapy for 6 months. It is important for your child to come for study visits (see virtual visit section below) once a month during the 6 months of berry therapy so the study can record your child's weight and adjust the amount given as your child grows. Once the berry/placebo therapy is complete, we will watch your child to see if the hemangioma comes back. These visits will occur every other month until your child is 12 months old and then another visit at age 15 months and at age 18 months.

To measure the microRNA 126 levels, the study staff or you (see virtual visits below) will collect at least 2 teaspoons of urine from the cotton balls, or urine bag, that you will be asked to place in your child's diaper. Medical history will be obtained at the first study visit. To measure hemangioma size, the study coordinator will use a tape measure or you will be given a measurement scale Photographs will also be taken to record changes in the appearance of the hemangioma. You will also be taught how to track the treatments on a drug diary. Each study visit will last 1-2 hours. The total number of study visits depends on the age of your child at the time of enrollment, with 8-10 visits in the first 12 months and 2 more visits at 15 and 18 months of age. Participation in the study ends at 18 months of age.

If you choose to get other treatments for your child's hemangioma, then participation in the study will stop at that time. This decision to withdraw from the study will not affect your child's access to care or other treatments for his/her hemangioma.

Task	Visit 1 day 1 (+/- 7 days)	Visit 2 d 30 (+/- 7 days)	Visit 3 d 60 (+/- 7 days)	Visit 4 d 90 (+/- 7 days)	Visit 5 d120 (+/- 7 days)	Visit 6 d150 (+/- 7 days)	Visit 7 d180 (+/- 7 days)	Visit 8 d240 (+/- 7 days)	Visit 9 d300 (+/- 7 days)	Visit 10 age 12m (+/- 7 days)	Visit 11 age 15m (+/- 7 days)	Visit 12 age 18m (+/- 7 days)
Medical History	X											
Photo	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X						
Measure	X	X	X	X	X	X	X	X	X	X	X	X
Urine	X	X	X	X	X	X	X	X	X	X	X	X
Dosing	X	X	X	X	X	X						

The urine tests may provide information that we were not specifically looking for in this study. This information is called "incidental findings." We will discuss these results with you if we believe that they may have a significant impact on your child's health or family's health. If you ask us to do so, we can also help you set up follow-up meetings with your child's regular doctor or other medical professionals not involved in this study who can discuss this information with you. These follow-up visits will not be part of this study. Therefore, you and your insurance company would be responsible for any fees and costs related to them.

Your child will not receive any money or other compensation for any new products that might be developed or sold from this research.

Virtual visits

There is the possibility of performing the visits virtually if desired. This includes telehealth study visits as well as curbside drop off/pickup of treatments/other related study samples. You will be able to decide which portions of the study you prefer to conduct in-person or virtually. An in-person first study visit is encouraged. If you choose to proceed with virtual visits, you will be given extra materials, video instructions, and handouts. You may be asked to switch from in-person to virtual visits, if it is deemed necessary by study staff.

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.

Although we will take every precaution, there is a small chance of loss of confidentiality of your child's study information.

All study medications may cause some side effects or other reactions. The side effects and discomforts most commonly associated with the medicine and procedures used in this study are listed below. There is no way to give absolute assurance that you will or will not experience any of these or other side effects.

The common side effects are purple discoloration of the skin where the cream was applied. This will go away in a couple days with bathing.
It is unlikely that the Pediaberry cream will cause any side effects or adverse events beyond skin discoloration.

Although children with berry allergies are excluded from participating in this study, an allergic reaction may occur. The symptoms of an allergic reaction can vary from mild to severe. If your child becomes exposed to an allergen for the first time, their symptoms may be mild. Symptoms of a mild allergic reaction can include; hives, itching, rash, scratchy throat, watery or itchy eyes. These symptoms may get worse if your child is exposed to an allergen many times. A severe and sudden allergic reaction can develop within seconds after exposure to an allergen. This type of reaction is known as anaphylaxis and results in life-threatening symptoms, including swelling of the airway, inability to breathe, and a sudden and severe drop in blood pressure. If your child experiences this type of allergic reaction, seek immediate emergency help.

Occasional side effects are skin irritation from the dressing adhesive, discomfort from removal of the dressing to hold the cream in place. This can be moistened with water to loosen it before removal, e.g. during bathing, to avoid discomfort. When bathing your child, the dressing may be removed and the Pediaberry contents wiped off immediately prior to bathing. Please wait at least five (5) hours after Pediaberry application before giving your child a bath.

If you are worried about anything while in this study, please call the study team at the telephone number on page 1 of this form.

Taking a placebo means that your child is not receiving the study medication. It is possible that there may be no change in your child's condition, and it could even get worse.

There may be other risks of being in this research study that are not known at this time.

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

Possible benefits to your child might be shrinkage of his/her hemangioma, and we might learn something that could help others in the future.

7) WHAT OTHER TREATMENTS OR OPTIONS ARE THERE?

Your participation is this study is voluntary. It is not necessary to participate in this study in order for you to get care for your condition. Other treatments such as topical and oral propranolol, oral steroids, steroid injections, surgical removal and laser therapy are available. If you decide not to be in this study, the study team will refer you to your regular doctor for care.

8) COSTS

All costs related to this study will be covered by the research team.

9) PAYMENT

A parking voucher will be provided each time your child comes in for a study visit.

For your time and inconvenience, your child (study participant) will receive $50 per completed study visit. You should receive this payment by pre-paid debit card within 24 hours of the completed study visit.

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

In the event of physical injury resulting from your participation in this study, 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.

11) 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, the study team will discuss it with you as soon as possible.

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

It is your choice to allow your child to be in this study. You may decide to stop allowing your child to be in this study at any time. If you decide to stop your child's participation in this study, call the study team at the number on page 1 of this form to see if there are any medical issues about stopping. If your child stops being in the study, there will be no penalty or loss of benefits to which your child is otherwise entitled.

If at any time the Principal Investigator believes that this study is not good for your child, the study team will contact you about stopping. If the study instructions are not followed, your child's participation in the study may also be stopped. If unexpected medical problems come up, the Principal Investigator or the Sponsor, the National Institutes of Health, may decide to stop your child's participation in the study.

13) OTHER IMPORTANT INFORMATION

It is important that you tell your child's other doctors about all medicines that your child is taking including the medicine being tested in this research study.

Being in more than one research study at the same time may cause injury. Tell us if your child is in any other research studies.

While your child is participating in this study, you may not be able to get access to your child's medical records related to this study because it could interfere with the results of the study. As soon as the study is finished, you will have access to these medical records.

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 Web site at any time.

If you are interested, the final study results will be shared with you once they are available. Please provide us with an email or address where we can send these results.

This study is being funded by (and the Principal Investigator is being paid by) the National Institutes of Health.

Indiana University 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 allow your child to participate in other research studies in the future. You have the right to decide to allow participation or decline participation in any future studies. We will not share your/your child's contact information with researchers outside Indiana University.

14) HOW WILL MY STUDY INFORMATION BE KEPT PRIVATE?

Efforts will be made to keep your child's personal information confidential. We cannot guarantee absolute confidentiality. Your child's personal information may be disclosed if required by law. No information which could identify your child will be shared in publications about this study.

Organizations that may inspect and/or copy your child's research records for quality assurance and data analysis include groups such as the study investigator and his/her research associates, the Indiana University Institutional Review Board or its designees, and (as allowed by law) state or federal agencies, specifically the Office for Human Research Protections (OHRP), the Food and Drug Administration (FDA) and the National Institutes of Health (NIH), etc., who may need to access your child's medical and/or research records.

For the protection of your privacy, this research is covered by a Certificate of Confidentiality from the National Institutes of Health. The researchers may not disclose or use any information, documents, or specimens that could identify you in any civil, criminal, administrative, legislative, or other legal proceeding, unless you consent to it. Information, documents, or specimens protected by this Certificate may be disclosed to someone who is not connected with the research:

(1) if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases);
(2) if you consent to the disclosure, including for your medical treatment;
(3) if it is used for other scientific research in a way that is allowed by the federal regulations that protect research subjects;
(4) for the purpose of auditing or program evaluation by the government or funding agency;
(5) if required by the federal Food and Drug Administration (FDA).

A Certificate of Confidentiality does not prevent you from voluntarily releasing information about yourself. If you want your research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to allow the researchers to release it.

15) WILL MY INFORMATION BE USED FOR RESEARCH IN THE FUTURE?

Information or specimens collected from your child for this study may be used for future research studies or shared with other researchers for future research. If this happens, information which could identify your child will be removed before any information or specimens are shared. Since identifying information will be removed, we will not ask for your additional consent.

16) WHAT WILL YOU DO WITH MY GENETIC INFORMATION?

This research follows the Genetic Information Nondiscrimination Act (GINA), a federal law that generally makes it illegal for health insurance companies, group health plans, and most employers to request the genetic information we get from this research and to discriminate against you based on your genetic information.

17) USE OF SPECIMENS

Because this is a research institution, specimens obtained in medical situations may later be used for research purposes. The investigator intends to include specimens taken from you along with other specimens that may also be used in an attempt to develop products to be sold, and it is not the intention of the investigator to enter into an agreement with you to become partners in sharing the profits or losses in the sale of those products.

18) WHAT FINANCIAL INTEREST DOES THE RESEARCHER HAVE?

One or more individuals involved in this study may benefit financially from this study. The Institutional Review Board (an ethics committee that helps protect people involved in research) has reviewed the possibility of financial benefit. The Board believes that the possible financial benefit is not likely to affect your safety and/or the scientific integrity of the study. If you would like more information, please ask the researchers or study staff.

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

For questions about the study or a research-related injury, contact the researcher, Dr. Gayle Gordillo, at 317-944-5283. After business hours, please call 317-944-5000 and ask the operator to page Dr. Gordillo.

If you are unable to reach the investigator at the above number(s) in an emergency, you may contact the Riley Hospital Pharmacy at 317-944-2335.

For questions about your rights as a research participant, to discuss problems, complaints, or concerns about a research study, or to obtain information or to offer input, please contact the IU Human Subjects Office at 800-696-2949 or at irb@iu.edu.

PARTICIPANT'S CONSENT

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

be given a copy of this informed consent document to keep for my records. I agree to allow my child to take part in this study.

Printed Name of Child Participant: _____

Date of Birth _____

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:** _____