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ASOCIACION BENEFICA PRISMA
JOHNS HOPKINS BLOOMBERG SCHOOL OF PUBLIC HEALTH
TULANE UNIVERSITY

INFORMED CONSENT DOCUMENT
Parental Consent

Study Title: PriDEC Perú: Lactobacillus reuteri DSM 17938 Phase 1 double-blind, placebo-controlled, single-trial study in children aged 2-24 months

Sponsor: National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institutes of Health of the United States

Research Institutions: Asociación Benéfica Prisma, Tulane University and the Bloomberg School of Public Health at Johns Hopkins University.

Principal Investigador in Peru: César Ramal Asayag, MD, Asociación Benéfica Prisma

Principal Investigators for PRIDEC Peru Project: Margaret Kosek, MD, JHSPH and Richard Oberhelman, MD Tulane University.

Institutional Ethics Committees: Asociación Benéfica Prisma (Perú) and Johns Hopkins Bloomberg School of Public Health.

CIEI / IRB No.: 00006724

Regulatory Authority in Perú: General Office of Research and Technology Transfer at the National Institute of Health of Perú.

Version and Date: 1.4 11-Aug-2017_English

Introduction:
We are inviting you to have your child participate in a clinical trial related to diarrhea in infants because you live in an area where diarrhea and its consequences are a frequent problem for children less than 24 months old. This clinical trial is part of a study called PriDEC Perú which is being carried out by researchers at Asociación Benéfica Prisma, Tulane University and the Bloomberg School of Public Health at Johns Hopkins University.

Your collaboration and your child's participation are completely voluntary and free. You can withdraw your participation at any time without affecting any of your rights. We are offering you more details about this clinical trial in this informed consent form.

This document explains the research study. Please take your time to carefully review it and to ask any questions that you deem appropriate, before confirming your child's participation. You can also ask questions at any time during the study. You can take an unsigned copy of this document with you, before confirming your child's participation, to read again and discuss the study with your family, friends, primary doctor or with anyone you want.

Justification, objectives and purpose of the research project:
As you know diarrhea is a common cause of illness and death among children in Peru. The primary goal of this study named PriDEC Perú, which has multiple phases, is to determine if giving treatment with live bacteria called *Lactobacillus reuteri* DSM 17938 to children while they have diarrhea will help them to recover faster. This bacterium is part of the group of bacteria known as probiotics which are similar to the bacteria used to make yogurt. Many people believe that these can have beneficial health effects. This probiotic is safe in adults and in healthy children between two and six years old. Our objective now with this clinical trial is to determine if it is also safe to give to children younger than 24 months which are the population most affected by diarrheal diseases. Similar probiotic bacteria has been used in children for many years without any evidence of safety problems but there have not been any formal safety studies in children between 2 and 24 months old.

Number of child participants to enroll:
This study will only occur in Loreto, Perú. We will enroll a maximum of 100 children to have a total of 60 participants: 30 boys and 30 girls between the ages of 2 and 24 months old.

Estimated duration of your child's participation in the study:
The total duration of the study is seven months and your child's participation would be for three months. We will give you more details on participation times during the study process.

Circumstances or reasons anticipated for which the study or a child's participation could be terminated
If the study product results in serious adverse events related to the medication, the study will be stopped early. Additionally if some of the bioethics committees that evaluate and monitor this study, or the sponsor, or the clinical trial regulatory agencies (INS in Perú) consider it to be justified. A child can be removed early from the study if decided by the principal investigator, one of the parents, or legal guardians.

Product being studied by the clinical trial

As previously explained, the product being investigated is a live bacterium called *Lactobacillus reuteri* DSM 17938 suspended in sunflower oil. As part of this clinical trial we will also use what is known in scientific terms as a placebo. This is a product that looks similar and has the same taste but does not have the probiotic bacteria. At the end of the study, we will compare the results from the children who received probiotics with those who did not receive it. The product was obtained from the BioGaia company in Stockholm, Sweden. Two billion doses of this probiotic have been given to people in 33 countries around the world. This bacteria (probiotic) has been given to newborns, children and patients with HIV without seeing any serious adverse effects. This bacteria is available to the public in the United States and in Europe. It is taken by thousands of people because they believe that it is a good product for preventing and reducing colic in children as well as a good treatment for diarrhea. In Perú, this probiotic from BioGaia is in the health registry and is sold in pharmacies on a national level as a dietary supplement.

Randomization and blinding

The fact that your child does or does not receive the product with probiotics is determined by a computer program and cannot be changed by the field team. This is what is known as randomization. Your child has twice as many chances of receiving the product with probiotics as of receiving the placebo. Neither you nor the health promoter nor the doctor evaluating it will know which study product your child is receiving. This is what is known as blinding. In case of emergency, a member of the research team will inform the doctor responsible for caring for your child which study product they have received.

Study procedures:

If you decide that your child will participate in the study and sign the consent form, a physician with the study will examine your child upon enrollment. They will also take a blood sample in order to evaluate the function of your child's kidneys and liver. We will also check to see if your child has anemia (low red blood cell count) and their white blood cell count. Additionally, we will test your child's blood for evidence of infection with HIV (the virus that causes AIDS). We will also ask you for a stool sample from your child before enrollment. The pre-selection period can last up to 14 days.

If any of these tests are outside the range of normal or if severe anemia or HIV infection is found, your child will not be able to participate in the study. We will inform you confidentially in a written report and the appropriate explanations will be provided by the research physician. If counseling is necessary, we will make sure you receive it and we will refer you and your child to a treatment center authorized by Perú's Ministry of Health.

In the case that all these tests are normal, then we will ask you to bring your child to the study clinic in Santa Clara for five consecutive days. A trained health worker will administer a daily dose of the study product during these visits in the clinic. Each one of these visits will take 20 minutes.

During the study, we will ask for blood samples from your child on three separate days. These days are: the day that your child begins to participate in the study, 5 days after starting to participate in the study (after the last dose of study product), and then 28 days after starting to participate in the study. On each of these days we will take a sample of no more than 2.5 ml (1/2 teaspoon). We do this to verify that the probiotic we give you is not harming your child's kidneys, liver, or blood.

We will also collect your child's stool once prior to taking the study product and then 8 times after taking the study product. We do this to determine if the probiotic we are giving you is detectable in your child's stool and for how long it remains detectable after your child stops taking it.

If you give us your consent in a separate document, we will keep the remaining blood and fecal samples to be used in future studies.

In the event that your child develops dysentery (diarrhea with blood), she or he will receive an antibiotic in addition to the study product. If your child has parasites in their intestines we will also treat them for this. If your child has anemia (low red blood cell count), we will provide treatment with iron after your child completes the 5 days of study product. This iron treatment will continue for 2 months, and we will check for anemia again at the end of that treatment with a blood test to count red blood cells using less than half a teaspoon of blood. If your child still has anemia, we will refer him or her to a local pediatrician at no cost to you or your family.

If your child develops a fever while taking the study product or in the four days that follow the enrollment day we will ask you to: 1) allow us to perform a blood test to determine if your child has malaria 2) allow that a doctor examine your child and 3) allow for 3 mL of blood to be drawn (about one and a half teaspoons) to determine if your child has an infection in the bloodstream. This blood test will also be used to test for malaria. The tests and any treatment given by the study team will be free for you.

You will have full access to the results as they are available. The study physician will inform you and explain the results to you as well as what actions to take.

We have prepared a calendar for you so that you can see when we will ask for blood and stool samples and on which days you can expect a home visit from a health promoter. These visits will occur over one month and each will last approximately 15 minutes.

Risks and discomforts related to the research study:

Your child's participation in this study has risks and disadvantages. First, in order to participate in the study your child must undergo blood tests at least three times (each time the amount of blood obtained will be no more than one-half teaspoon). Obtaining a blood sample requires blood to be obtained from a vein, a finger stick, or a heel stick. The method used for blood collection will depend on your child's age and your preference. This is uncomfortable, but is unlikely to cause any problems besides discomfort at the moment the sample is obtained. Occasionally fear will cause your child to feel dizzy or faint but this passes quickly with no lasting effects. Rarely, a bruise or infection may occur at the site from which blood was obtained. The health workers are well trained to minimize this risk. Additionally, if this occurs then they will provide any care necessary to treat the bruise or infection at no cost to you.

We will also ask for a sample of your child's stool during the course of the study. This can be considered inconvenient, but poses no risk to their health.

If your child participates in this study, he or she will visit the study clinic for 5 days. Then we will make home visits every three to five days until 31 days after receiving the study product for five days. A final visit will occur 3 months after your child's first dose of the study product. These visits are relatively short and you can coordinate the best time with the health promoter to minimize any inconvenience.

It is possible that your child can experience a complication from taking a live probiotic. This is unlikely but your child could develop a serious bloodstream infection or disease caused by the product under investigation. It is also possible that your child has difficulty breathing as a result of the probiotic producing acid (a condition called lactic acidosis). It is also possible that your child is allergic to the oil that we give which could form into a skin rash or they could have difficulty breathing after taking it. We will visit you frequently to monitor the possible adverse effects that could result from participating in this clinical trial.

Your commitment by allowing your child to participate
Upon accepting your child's participation in this clinical trial you are committed to completing all of the noted procedures for the study and of being available for the established visits for three months in addition to being sincere and honest with the members of the research team. You should also be committed to informing us of any event related to your child's health during the study period.

Alternatives to processes and medications
The alternative is for your child to not participate in the study. Your child is not obligated to participate in this study at this moment or in the future. If you decide that your child is

participating now, you can also withdraw them at any moment and for any reason without harm, punishment, or any payment on your behalf from you or your family.

Benefits derived from the study

The first step in developing any treatment for use in children is by testing it in healthy children- your child's participation therefore is in the first phase of the development of this treatment ultimately aimed at improving the treatment of diarrhea in children. Your child's participation in this study allows us to further test the probiotic *Lactobacillus reuteri* DSM 19738 if we demonstrate that the substance is safe. Your child will not individually receive any direct health benefits from their participation.

Indemnity and treatment in case of harm or injury from your child's participation in this research

All of the procedures, lab tests, medical attention and medications that your child needs as part of the procedures for this study or as a result of their participation will be completely free. You will not pay anything. Medical attention will be provided by the Asociación Benéfica Prisma Policlínico in Santa Clara de Nanay. If your child requires hospitalization or medical procedures that are not available at the clinic during the study period, you will be transferred to the Selva Amazónica clinic in Iquitos where you will receive the necessary medical attention without any cost to you. If this happens, the costs of your displacement and upkeep will be covered. We have an insurance policy of up to 250,000 dollars. This insurance is in effect during the study period and will give financial compensation to participants in case of a serious adverse event related to participating in the clinical trial.

We are committed to informing you of any new discoveries and updated information about this research product even though this could affect your desire for your child to continue participating in this clinical research.

You will have complete access to all results when they become available. The research physician will inform you and explain the results. During the study, all of the information referring to your child's health and the research product will be analyzed by a group of experts to determine if the investigation product is safe. The study will be stopped if the product under investigation produces serious adverse effects.

Costs and payment

All of the procedures, laboratory tests, medical attention and medications that your child needs as part of the process for this study or as a result of their participation in this trial will be completely free for you. Any displacement of you and your child caused by participating in the study and the upkeep derived from a possible hospitalization will be free for you.

You and your child will not receive any money for your participation in this study now or at any time in the future. To compensate you for your time and inconvenience from our

visits, we will give you a water storage container, a small food basket with milk, rice, oil, beans and noodles and a small toy for your child after completing the initial evaluation. On the fifth dosage day of the study product we will offer your child another toy. On the 28th day of the study you will be given a second basket and another toy for your child.

Privacy and confidentiality:
We will respect your privacy and your child's privacy. For this clinical trial, only the information you provide during the interviews in the study clinic, the home visits and the analysis of samples. If your child requires hospitalization, the clinical history at the center where they are receiving care will be accessed. Information on you or your child will not be accessed during this clinical trial from other sources.

The forms used to collect data will be stored in a private laboratory inside of locked cabinets in areas with restricted access. The forms will be coded and entered into a data system without using the names of you or your child and in a way where you cannot be identified.

The data gathered and all biologic samples will only be available to the study team, the Peruvian National Institute of Health (INS), NIDDK and a monitoring committee comprised of a group of experts in clinical research and related fields who will evaluate the quality and safety of this clinical trial.

The participation of you and your child in this clinical trial are completely voluntary. You have the right to decide if your child participates in this study. If you decide to participate in this clinical trial now and then change your mind later, you can suspend your child's participation at any time. The data would be eliminated and the samples would be destroyed at your request.

Results published or presented publicly will not have names or any other information that could identify you.

Condition after the end of the clinical trial, post-study access to the research product
Participation in this clinical trial does not allow you to obtain for free the *Lactobacillus reuteri* DSM 19738 that is commercially available in pharmacies around the country. The researchers for this clinical trial do not have any financial or commercial ties to the company that makes or sells the product and will not offer it outside of the study period. You will not receive any financial benefit for any product or idea created by the researchers using the data or materials obtained from you or your child.

Information on the clinical trial
A description about this clinical trial is available at www.clinicaltrials.gov as required by U.S. law. This website will not include information that could identify you. Information about

this study is also available at the REPEC which is accessible at www.ensayosclinicos-repec.ins.gob.pe. You can review these web sites at any time.

The final results from this clinical trial will be published in a scientific publication once all of the data has been analyzed. This should happen between six months and one year after all of the follow up for the final participant has been done. You will receive a summary with the more prominent results in Spanish and non scientific language once the scientific article has been published.

Contact Information: Who do I call if I have questions or problems?
You can ask questions or report damages related to the research to Dr. Cesar Ramal Asayag, the principal investigator, or to Maribel Paredes Olórtegui, the study coordinator now or in the future by calling the number in Iquitos: 234250 or by personally going to 622 Calle Ramírez Hurtado in Iquitos. You can also send an email to this address: mparedeso@prisma.org.pe

If you have a medical emergency, you should go directly to the nearest health post or hospital.

For questions about your rights as a research participant or for any kind of complaint, contact the office of the Asociación Benéfica Prisma ethics committee whose president is Dr. Salomón Zavala Sarrio. You can call the number in Lima: 01- 209-0400 Ext. 246, write an email to this address: mmateo@prisma.org.pe or mail a letter to this address: Carlos Gonzáles 251 San Miguel, Lima 32.

If you think that your rights are violated or to make a complaint, you can contact the INS (General office of research and technology transfer, OGITT), the regulatory body for clinical trials, at the following number: 01-7481111 ext 2191 or by email at the following address: consultaensayos@ins.gob.pe or by presenting a formal document through the documents reception center at the institution or by personally going to the OGITT at the following address: Cápac Yupanqui 1400, Jesús Maria, Lima 11.

What does my signature (or thumbprint) on this consent form mean?

I, _____
and _____ father
and mother of: _____ .

- I have read (or someone has read me) the information provided in this document.
- I have been informed about this study's objectives, procedures, risks, my rights and know what is expected of me.
- I have been able to ask questions about the study and all of them have been adequately answered. I think that I understand all of the information provided about this clinical trial.
- I understand that my participation and my child's participation are voluntary.
- I understand that I can withdraw my child from the study when I want, without giving any explanation and without this affecting our medical care.
- Upon signing this document, I accept my child's participation in this clinical trial. I am not renouncing any rights.
- I understand that I will receive a signed copy of this document with the date.
- I understand that Dr. Kosek, Dr. Ramal or Dr. Oberhelman can suspend my child's participation in the study if they do not think them to be appropriate for this study.
- I understand that Dr. Kosek, Dr. Ramal Asayag, or Dr. Oberhelman can discontinue my child's participation in the study if they feel that he or she is not suited for the study.
- I agree to cooperate with Dr. Ramal Asayag and the members of the research group. I will inform them immediately if my child feels any unexpected or unusual symptom.
- I understand that Tulane University and the Johns Hopkins School of Public Health are not responsible for damages or adverse effects not related to participation in this clinical trial.
- I understand that in the event my child has health problems as a result of their participation in this clinical trial, the Asociación Benéfica Prisma and the principal researchers are responsible for the compensation owed as determined by the Peruvian Supreme Decree No 006-2007-SA Article 27.

Print name of child participant

Print name of Mother	Signature of Mother	Date	Time
Print name of Father	Signature of Father	Date	Time

	Ask the participant to mark a “left thumb impression” in this box if the participant (or participant’s parent) is unable to provide a signature above.

I have been a witness to the exact reading of the informed consent to the parents of the potential research subjects and they have been given the opportunity to ask questions. I confirm that they have given their consent freely.

Name of the witness	Witness Signature	Date	Time

I have explained the clinical trial to the parents of the research subject and have answered all of their questions. I confirm that they understand the information described in this document and accepts their child’s participation.

Name of the researcher	Researcher Signature	Date	Time

Signed copies of this document should be: 1) kept archived by the principal investigator, 2) delivered to the participants and 3) placed in the research and medical registry for the participant. The consent document is not valid without the stamp of approval of the ethics committee.

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Informed consent for the use of specimens for future research

We would like to store blood and stool samples obtained in this study for future studies related to health, immunity to disease (ability to fight infection), and nutrition. If you give us permission to store your child's sample for future research, we may share it with other investigators although we will never give them information that would allow them to identify you or to contact you or your child. These samples may also be used to develop diagnostic tests for different kinds of diarrheal diseases or to better understand normal bacteria living in the intestine.

Please read the sentence below and select an answer---

1) My child's blood and stool sample may be kept for research related to health, resistance or natural defenses against disease, nutrition, and the microbiome
   YES NO (mark one answer only)

I understand that if in the future I decide that I no longer wish to have my child's stool or blood plasma used for any purpose not directly related to the study I can do so without affecting my child's access to health care or participation in the study.

Print name of child participant			
Print name of Parent/Legal Guardian	Signature of Parent/Legal Guardian	Date	Time
Print name of Parent #2 for	Signature of Parent #2	Date	Time
Print name of Witness (if parent or guardian unable to read/write)	Signature of Witness	Date	Time
Print name of Person Obtaining Consent	Signature Person Obtaining Consent	Date	Time

☐ Ask the participant to mark a "left thumb impression" in this box if the participant (or participant's parent) is unable to provide a signature above.

Signed copies of this consent form must be: 1) retained on file by the principal investigator, 2) given to the subject and 3) placed in the subject's research/medical record. Consent document is not valid without the IRB stamp of approval.