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IRB Number: 00002431

Title: Mechanisms of Preventing Antibiotic-Associated Diarrhea and the Role for Probiotics

Document: Informed Consent Form

Document Date: 05/13/2021 (Approval)

Study number: 00002431 Principal Investigator (s): Daniel J. Merenstein MD

Title: Exploratory Pilot Studies to Demonstrate Mechanisms of Preventing Antibiotic-Associated Diarrhea and the Role for Probiotics (R33)

Permission to Take Part in a Human Research Study

Georgetown University

Location: Georgetown University

Key Information: The following is a short summary of this study to help you decide whether or not to be a part of this study. More detailed information is listed later on in this form.

Why am I being invited to take part in a research study?

You are invited to consider participating in this study. The study is called "Exploratory Pilot Studies to Demonstrate Mechanisms of Preventing Antibiotic-Associated Diarrhea and the Role for Probiotics." Please take your time to make your decision. Discuss it with your family and friends. It is important that you read and understand several general principles that apply to all who take part in our studies:

- Taking part in the study is entirely voluntary;
- Personal benefit to you may or may not result from taking part in the study, but knowledge may be gained from your participation that will benefit others; the purpose of this study is not to benefit you individually but to gain knowledge that may help others in the future.
- You may decline to participate or you may withdraw from the study at any time without loss of any benefits to which you are entitled and without jeopardizing your access to care, treatment and health services unrelated to the research

The purpose and nature of the study, possible benefits, risks, and discomforts, other options, your rights as a participant, and other information about the study are discussed below. Any new information discovered, at any time during the research, which might affect your decision to participate or remain in the study will be provided to you. You are urged to ask any questions you have about this study with the staff members who explain it to you. You are urged to take whatever time you need to discuss the study with your physician, hospital personnel and your family and friends. The decision to participate or not is yours. If you decide to participate, please sign and date where indicated at the end of this form. The research is being sponsored by the National Center for Complementary and Integrative Health (NCCIH), a part of the National Institutes of

Health (NIH). NCCIH is called the sponsor and Georgetown University is being paid by NCCIH to conduct this study with Dr. Daniel Merenstein, MD as the principal investigator.

What should I know about a research study?

- Someone will explain this research study to you.
- Whether or not you take part is up to you.
- You can choose not to take part.
- You can agree to take part and later change your mind.
- Your decision will not be held against you.
- You can ask all the questions you want before you decide.

Why is this research being done?

The main purpose of this study is to better understand how consuming a probiotic ("friendly bacteria") can change or restore your gut microbiota (a Collection of microorganisms —bacteria, fungi, viruses, etc.—— which live in our gut and gastrointestinal tract) after it has been affected by antibiotic use. We will compare this to those who take a control yogurt without the added probiotic. This research is being done because it has been shown that antibiotics typically decrease the number and type of bacteria in your gut microbiota, which may result in diarrhea. Sometimes probiotics are recommended to prevent diarrhea but we do not know exactly why or how your gut microbiota changes from the probiotic or from antibiotics.

One way that we can learn more about your microbiota is through fecal (stool) samples collected at different times before and during probiotic and antibiotic use. We will conduct genetic tests of your samples and measure any changes in the amount, number, and different types of microorganisms and short—chain fatty acids (SCFA), which are produced from fermentation, a digestive process that takes place in your intestines. We hope by learning more about how probiotics and antibiotics affect your gut microbiota and SCFA, we will be able to help improve the health of patients taking antibiotics in the future. You are being asked to participate in this study because you are a reasonably healthy adult. Additionally, you are eligible to participate in this study if:

1) You are between the ages of 18-65 years;
2) You are able to read, speak, and write in English or Spanish;
3) You have access to a refrigerator for proper storage of the yogurt products; and
4) You have telephone access.

You may not participate in this study if any of the following apply to you: 1) were a participant in the Yobiotic study, you have 2) diabetes or asthma that requires daily medication, 3) allergy to strawberry, 4)

active diarrhea (defined as three or more loose stools per day for two consecutive days), 5) any gastrointestinal medications, i.e. medicines for irritable bowel syndrome, gastroesophageal reflux disease, inflammatory bowel disease, etc. (a full medication list will be reviewed by the study investigator before enrollment, 6) lactose intolerance, 7) history of heart disease, including valvulopathies or cardiac surgery, any implantable device or prosthetic, 8) history of gastrointestinal surgery or disease, 9) milk-protein allergy, 10) allergy to any component of the product or the yogurt vehicle, 11) allergy to penicillin or cephalosporin class antibiotics, 12) allergy to any of the following medications: a. penicillin, b. Erythromycin, c. Trimethoprim, d. Tetracycline, or e. Ciprofloxacin, or 13) currently breastfeeding, pregnant, or planning to become pregnant during the study.

You will also be asked to refrain from antibiotics and any probiotic foods or supplements for at least 30 days prior to the collection of the first baseline stool sample until the completion of the 30-day study period. You will be supplied with a list of these products.

How long will the research last and what will I need to do?

We expect that you will be in this research study for approximately 8 weeks. You will be asked to do the following:

The first 30 days will be the period where you avoid all antibiotics and probiotic products (run-in). You will start the antibiotic and yogurt after these 30 days (called Day 1). You will finish taking the antibiotics on Day 7 and drinking the yogurt on Day 14. At days 21 and 30, you will be asked to provide stool samples as well as information about your health during this period. If you begin any antibiotics during the 30-day run-in period (but otherwise still qualify for the study), once you complete your antibiotics course we may ask you to extend your run-in period to a full 30 days before starting the yogurt.

The researcher may decide to take you off this study if circumstances arise concerning your medical best interest, funding is stopped, the treatment supplies are insufficient, your condition worsens, or new information becomes available.

You can stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to the researcher and your regular doctor first.

More detailed information about the study procedures can be found under ***"What happens if I say yes, I want to be in this research?"***

Is there any way being in this study could be bad for me?

The most common risks and side effects related to the probiotic and non-probiotic cultured yogurt include: allergic reaction to drink ingredients, most likely strawberry, or digestive problems such as stomachaches or loose, watery bowels due to lactose intolerance.

Potential risks and side effects related to the amoxicillin-clavulanate administration most commonly include: nausea and/or vomiting, diarrhea, upset stomach and mild to severe skin rash.

More detailed information about the risks of this study can be found under ***"Is there any way being in this study could be bad for me? (Detailed Risks)"***

Will being in this study help me in any way?

We cannot promise any benefits to you or others from your taking part in this research. However, we hope the information learned from this study will benefit others in the future.

If you agree to take part in this study, there may or may not be direct medical benefit to you. We cannot promise that you will personally experience medical benefits from participating in this study. The main purpose of this study is to gain knowledge on how probiotics and antibiotics affect the gut microbiota and SCFA.

What happens if I do not want to be in this research?

Participation in research is completely voluntary. You can decide to participate or not to participate. Your alternative to participating in this research study is to not participate.

Detailed Information: The following is more detailed information about this study in addition to the information listed above.

Who can I talk to?

If you have questions, concerns, or complaints, or think the research has hurt you, talk to the Project Coordinator, Keisha Herbin Smith, at 202-687-6454, or Daniel Merenstein, MD at 202-687-2745.

This research has been reviewed and approved by an Institutional Review Board ("IRB"). You may talk to them at (202) 687-1506 or irboard@georgetown.edu if:

- Your questions, concerns, or complaints are not being answered by the research team.

- You cannot reach the research team.
- You want to talk to someone besides the research team.
- You have questions about your rights as a research subject.
- You want to get information or provide input about this research.

How many people will be studied?

We expect about 130 people will be in this research study recruited from the Washington, DC metropolitan area.

What happens if I say yes, I want to be in this research?

Once it is confirmed that you meet all inclusion and exclusion criteria, baseline data will be collected. These include your Baseline Health Status and Demographic Information.

Once enrolled, you will be asked to avoid antibiotics and any probiotic foods or supplements for at least 30 days prior to starting the study (called the “run—in" period) until the completion of the 30-day study period. You will be asked to provide one stool sample before the run-in period, and one stool sample about 30 days after you enroll, prior to starting the antibiotics and yogurt. During this run-in period, we will also call twice to ask what you have eaten in the previous 24 hours (this is called a "diet recall"). You will collect stool samples multiple times throughout the study, one each on Days 7, 14, 21 and 30 (±2 days). Research staff will be trained on how to properly transport stool from your home and how to instruct you on collecting stool.

Following the baseline procedures and 30-day “run-in" period, we will confirm you still meet the inclusion and exclusion criteria and ask your Post Run-In Health Status. If you are still eligible, you will take a 7-day course of antibiotics, amoxicillin-clavulanate (875mg). You will also be "randomized" into one of five study groups: 1) Bifidobacterium animalis subsp. lactis BB-12 (BB-12) probiotic supplemented yogurt taken either at the same time or 2) four hours after the amoxicillin-clavulanate, 3) control yogurt without the added probiotic taken either at the same time or 4) four hours after the amoxicillin-clavulanate, or 5) no yogurt at all (amoxicillin-clavulanate only). You will have roughly a 45% chance of being placed in one of the probiotic groups, a 45% chance of being placed into one of the control yogurt groups, and 10% chance of being in the no yogurt group.

If you are in one of the yogurt groups, you will then receive the probiotic yogurt or control yogurt for days 1 through 14 to be consumed by mouth once a day. The amount of probiotic supplemented yogurt drink to be supplied will be 4 ounces per day, which is slightly more than 100 grams/day. We will supply you with a

measuring cup to measure the daily dose. During the initial visit, participants will also be given all the materials to collect stools, daily diary, and other study forms and materials, as well as the initial payment.

We will also ask a form called the Gastrointestinal Symptom Rating Scale (GSRS) on Days 1, 7, and 14 (±2days), which Is a quality of life questionnaire. Follow-up phone calls will be completed on Days 7, 14, and 30 (±2 days). It is important that all visits be completed in a timely and regular fashion. Generally, the Follow-Up Form will be the only form completed during the phone calls, but at times depending on your report, there may be another form or two. The follow-up period includes all the time previous to the day of the interview. Any incidents that happen the day of the visit would be captured in the next follow-up visit.

There will be a set day that each subsequent visit should be completed. The research personnel will call at least one time per day for 3 business days or until the data is collected. If more than 3 business days have passed from the set day, you may be asked to provide any information at the next upcoming call.

You will keep a daily diary to track the number of bowel movements, if antibiotic or yogurt was consumed on that day, number, shape and consistency of your stools, health, use of other medicines or products, adverse events, and quality of life.

You will be asked to advise the researchers of any medications you are taking. in addition, if you are taking any over-the-counter drugs or herbal supplements which you have obtained from the drug store, grocery store, etc., you should advise the researchers.

The stool samples you collected throughout the study will be shared with two partner laboratories for testing. These tests will help us to learn more about any changes in your microbiota and short-chain fatty acids after taking the antibiotics and yogurt. The microbiota tests will be performed in Dr. Claire Fraser's laboratory at the Institute for Genome Sciences, a part of the University of Maryland School of Medicine, and the short-chain fatty acid tests will be performed in Dr. Maureen Kane‘s laboratory at the University of Maryland School of Pharmacy. Genetic testing of stool microbes will also be done to better understand the changes in microbiome composition through the course of the study. Any samples and data shared with our partners will only be identified by a unique study code, meaning that we will not share your name, address, or any information that can reveal your identity.

The group you will be in will be chosen by chance, like flipping a coin. Neither you nor the study doctor will choose what group you get. You will have roughly a 45% chance of being placed in an active yogurt group, 45% chance of being in a control yogurt group, and 10% chance of being in a non-yogurt group. Neither you nor the study doctor will know which yogurt you are getting.

What are my responsibilities if I take part in this research?

If you take part in this research, you will be responsible for:

- Refraining from consuming any yogurt or food products or supplements that contain probiotics, and antibiotics.
- Participating in follow up calls on the specified days.
- Collecting stool samples on the specified days.
- Consuming your assigned yogurt (if any) and antibiotics as specified by the protocol.
- Record the day and time of consumption for your yogurt (if any) and antibiotics.

What happens if I say yes, but I change my mind later?

You can leave the research at any time it will not be held against you.

If you stop being in the research, already collected data may not be removed from the study database. You will be asked whether the investigator can collect data from your routine medical care. If you agree, this data will be handled the same as research data.

Is there any way being in this study could be bad for me? (Detailed Risks)

The most common risks and side effects related to the probiotic and non-probiotic cultured yogurt include: allergic reaction to drink ingredients, most likely strawberry, or digestive problems such as stomachaches or loose, watery bowels due to lactose intolerance.

Potential risks and side effects related to the amoxicillin-clavulanate administration most commonly include: nausea and/or vomiting, diarrhea, upset stomach and mild to severe skin rash.

The most serious potential risk is diarrhea caused by a Clostridium difficile infection. Occasionally, antibiotics result in an overgrowth of a potentially dangerous bacterium called "Clostridium difficile", a bacterium that is naturally present in the guts of some humans. This is also known as 'C. difficile' or 'C. diff,' and can cause a severe and life-threatening diarrheal illness that may require additional medical treatment.

A small minority of patients who take an antibiotic will get an infection due to C. difficile, and some people, such as those over 65 years of age and those who have a history of gastrointestinal disease, have a greater risk for C. difficile infection than others. To minimize this risk, you may only enroll in this study if you are generally healthy, 65 years of age or under, and do not have gastrointestinal disease. Although all types of antibiotics can potentially result in a Clostridium difiicile infection, the type of antibiotic used in this study is generally not considered as high risk for Clostridium difficile infection.

While severe C. difficile infections are rare, we will be asking you about your symptoms throughout the study. Symptoms of C. difficile infection include stomach pain or tenderness, bloody stools, fever, nausea, and diarrhea. If you experience symptoms you think may be due to C. difiicile infection, call your personal doctor and alert them about your participation in this study. Please also alert a member of the study team.

Risks and side effects related to stool collection include: there is no known risk to stool collection. However, there may be some discomfort with collecting stool samples.

There may also be side effects, other than those listed above that we cannot predict. Other drugs may be given to make side effects that occur less serious and less uncomfortable. Many side effects may go away shortly after the yogurt consumption is stopped, but in rare cases side effects can be serious, long lasting or permanent.

Anyone who develops evidence of allergy or hypersensitivity to any component of the investigational product or treatment antibiotic will be withdrawn from the clinical study and receive no further doses of either probiotic or antibiotic. In addition, we will continue to follow these participants for safety for the remainder of the study.

For more information about risks and side effects, ask the researchers.

In addition to these risks, this research may hurt you in ways that are unknown. These may be a minor inconvenience or may be so severe as to cause death.

Avoidance of Pregnancy: The medicines and procedures used in this study may be unsafe for a fetus/ unborn baby, an infant, sperm, and eggs. If you, as a subject of study, are a woman of child bearing potential, you must agree to avoid pregnancy during your participation in this study. In addition, if you are already pregnant or are breastfeeding, you cannot participate in this study.

We do not ask that men enrolled in the study make any change of lifestyle or family planning during the study.

Taking part in this research study may lead to added costs to you if you suffer any adverse event.

Policy/Procedures or Research Related Injuries

The Policy and Procedure for the Sponsor, NCCIH, are as follows:

The sponsor, NCCIH, will not pay for care necessitated by a research related injury.

The Policy and Procedure for Georgetown University Medical Center are as follows:

We will make every effort to prevent study-related injuries and illnesses. If you are injured or become ill while you are in the study and the illness or injury is due to your participation in this study, you will receive necessary medical care. The costs of this care will be charged to you or your third party payor (e.g., your health insurer) in the usual manner and consistent with applicable laws. No funds have been set aside by Georgetown University, Georgetown University Hospital, MedStar Health Research Institute, or their affiliates, to repay you or compensate you for a study related injury or illness.

Risks associated with the genetic information:

Risks of participating in research involving genetic testing include the use of personal, genetic information for unauthorized or discriminatory purposes. All research personnel who will have access to genetic information about you are ethically and legally obligated to maintain the confidence of that information. However, there can be no absolute guarantees that the genetic information will remain confidential.

A federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally offers the following protections:

- Health insurance companies and employer-based group health plans may not request your genetic information that we get from this research.
- Health insurance companies and employer-based group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.
- Employers with 15 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

Be aware that this law does not protect you against discrimination on the basis of your genetic information by companies that sell life insurance, disability insurance, or long-term care insurance.

In addition, there is a risk that being in a genetics study can cause psychological distress or tension with other family members.

What happens to the information collected for the research?

Efforts will be made to protect your medical records and other personal information to the extent allowed by law. However, we cannot guarantee absolute confidentiality. Records of research study participants are

stored and kept under physical lock and password protection. If information about your participation in this study is stored in a computer, we will take the following precautions to protect it from unauthorized disclosure, tampering, or damage: We will make our best effort to keep all data confidential. Alphanumeric codes will be assigned to participants on enrollment. All questionnaires will be identified by this unique code. Research personnel will keep questionnaires and data sheets containing identifiable information in separate locked cabinets or in a password—protected database. No identifiable information will be allowed outside the secure location. All databases will be password protected to ensure that only study personnel can access the data. The secure servers used for this study are maintained at Medstar Health Research Institute's data center.

The stool samples you collected throughout the study will be shared with two partner laboratories for testing. These tests will help us to learn more about any changes in your microbiota and short-chain fatty acids after taking the antibiotics and yogurt. Genetic testing of stool microbes will also be done to better understand the changes in microbiome composition through the course of the study. The microbiota tests will be performed in Dr. Claire Fraser's laboratory at the Institute for Genome Sciences, a part of the University of Maryland School of Medicine, and the short-chain fatty acid tests will be performed in Dr. Maureen Kane's laboratory at the University of Maryland School of Pharmacy. Any samples and data shared with our partners will only be identified by a unique study code, meaning that we will not share your name, address, or any information that can reveal your identity.

You will not be identified in any reports or publications resulting from this study. In addition to the researchers and research institution(s) conducting this study, organizations that may request to inspect and/or copy your research and medical records for quality assurance data analysis and other research related and operational or administrative purposes, include groups such as: NCCIH, Food and Drug Administration, Georgetown University, Georgetown University Institutional Review Board (IRB), federal research oversight agencies.

Please note that administrative personnel involved in processing your payment for participation will be aware of your identity.

We may publish the results of this research. However, we will keep your name and other identifying information 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 you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Federal law provides additional protections of your medical records and related health information. These are described in an attached document.

HIPAA Authorization

We are committed to respecting your privacy and to keeping your personal information confidential. When choosing to take part in this study, you are giving us the permission to use your personal health information including the health information in your medical records and information that can identify you. For example, personal health information may include your name, address, phone number or social security number. The health information we may collect from you and use for this research includes:

- Medical history to make sure you qualify for study
- Basic information about you, such as age, race, etc.
- Lab tests, or certain health information indicating or relating to a particular condition as well as diaries and questionnaires, such as loose stools, stomach pain, etc.
- Records about study medication or drugs
- Genetic health information: collected from stool sample microbes.

Once we have the health information listed above, we may share some of this information with the following offices or entities outside of Georgetown University and its clinical partners (or affiliates): the Georgetown University Office for Research Integrity; the US Office of Research Integrity; the US Office for Human Research Protections; the US Food and Drug Administration.

Any research information shared with outside entities will not contain your name, address, telephone or social security number or any other personal identifier unless disclosure of the identifier is necessary for review by such parties or is required by law or Georgetown University policy [except that such information may be viewed by the Study sponsor and its partners or contractors at the Principal Investigator's office].

The following entities may receive your health information:

- Authorized members of the Georgetown University MedStar Health workforce, who may need to see your information, such as administrative staff members from the Georgetown University Institutional Review Board (IRB) Office and it's agents, and members of the Institutional Review Board.
- Laboratories and other individuals and organizations that may need to see your health information in connection with this study.
- Other Georgetown University and MedStar Health research centers and Georgetown University and MedStar Health contractors contractors who are also working on the study.
- Study monitors and auditors who make sure that the study is being done properly,

- The NCCIH, who is sponsoring the study, and that company's contractors and partners.
- Government agencies and public health authorities, such as the Food and Drug Administration (FDA) and the Department of Health and Human Services (DHHS).
- Others*:*

Those persons who get your health information may not be required by Federal privacy laws (such as the Privacy Rule) to protect it. Some of those people may be able to share your information with others without your separate permission.

The results of this study may also be used for teaching, publications, or for presentation at scientific meetings.

Unless you revoke your consent, it will expire in one year. After the expiration date, Georgetown University may not gather new information about you, or use or disclose your personal health information collected in this study for any purpose other than the research study described in this consent unless Georgetown University obtains permission to do so from you.

Although you may revoke consent to participation in this research at any time and in any format, you must revoke authorization for use or disclosure of your health information in writing. To revoke your authorization, write to:

PI's Name: Daniel Merenstein, MD
Institution: Georgetown University
Department: Family Medicine
Address: 4000 Reservoir Road NW, Washington, DC, 20007.

You do not have to authorize the use or disclosure of your health information; however, you will not be allowed to take part in this research study if you do not allow this. If you do not authorize the use or disclosure of your health information, it will not affect your treatment by health care providers, or the payment or enrollment in any health plans, or affect your eligibility for benefits.

A copy of this signed consent document, information about this study, and the results of any test or procedure done may be included in your medical records and may be seen by your insurance company.

Can I be removed from the research without my OK?

The person in charge of the research study or the sponsor can remove you from the research study without your approval. Possible reasons for removal include:

- They judge that it is in your best interest to do so.
- You experience a study-related injury.
- You need additional or different medication.
- You do not comply with the study plan.
- They may remove you from the study for various other administrative and medical reasons.

What else do I need to know?

The research is being sponsored by The NCCIH. The NCCIH is called the sponsor and Georgetown University is being paid by the NCCIH, to conduct this study with Dr. Daniel Merenstein as the primary investigator.

If you agree to take part in this research study, we will pay you up to $120 ($20 per stool sample collected) for your time and effort.

Instead of being in this research study, your choices may include: Not participating

Your information and samples (both identifiable and de-identified) may be used to create products or to deliver services, including some that may be sold and/or make money for others. It is the policy of Georgetown University not to provide financial compensation to you should this occur.

Making your choice

Please read the sentence below and think about your choice. Please check "Yes" or "No" then add your initials and date after you answer. **No matter what you decide to do, it will not affect your care.** If you have any questions, please talk to Dr. Merenstein or the project Coordinator, or call the Institutional Review Board at 202-687-1506.

I give my permission for my stool samples to be stored for future use by the study investigators. I give authorization for my accompanying health information to be used and disclosed as marked below:

1. I give permission for my stool samples to be kept by the study investigators for future research to learn more about antibiotic-associated diarrhea, antibiotic use and/or probiotics.

Yes **No**

Initials	Date

2. I give permission for my stool samples to be kept by the study investigators for future research to learn more about other health problems.

Yes No

Initials	Date

IRB Approval Date

CR00002083
IRB Approved
5/13/2021 - 5/12/2022

Study number: 00002431 Principal Investigator (s): Daniel J. Merenstein MD

Title: Exploratory Pilot Studies to Demonstrate Mechanisms of Preventing Antibiotic-Associated Diarrhea and the Role for Probiotics (R33)

Signature Block for Capable Adult

Your signature documents your permission to take part in this research.

Signature of subject	Date
Printed name of subject	
Signature of person obtaining consent	Date
Printed name of person obtaining consent	IRB Approval Date

IRB Approval Date

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5/13/2021 - 5/12/2022