Informed Consent Form
And
Authorization To Use And Disclose Protected Health Information

Sponsor / Study Title:	**Entrinsic Bioscience, LLC / "An evaluation of tolerability with daily consumption of EBS Advanced IBS-D among patients with diarrhea predominant irritable bowel syndrome (IBS-D): A pragmatic open-labelled home use study."**
Protocol Number:	**EBSIBSD1**
Principal Investigator:	**WIlliam Denman, MD, FRCA**
Telephone:	
Address:	**Entrinsic Bioscience, LLC** **500 River Ridge Drive** **Norwood, MA 02062**

STUDY SUMMARY

In this study, eligible participants who have been diagnosed with diarrhea predominant irritable bowel syndrome (IBS-D) will be provided an investigational product (EBS Advanced IBS-D) which they consume twice a day for a 2-week period.

Over the course of the study, participants will answer questions about their experience with the study product and any impact it may have on their IBS-D. In addition, they will be asked to keep a short daily study diary to record IBS-D symptoms and study product use. These questionnaires are available as an application that can be accessed on a mobile device and take less than 15 minutes a day to complete.

This informed consent document will provide you with important information about this study. You must review the entire document. It will describe the study's purpose, the procedures and methods involved, and any potential benefits and risks that are involved if you chose to participate in the study. It will also explain your right to withdraw from the study at any point. Your participation in this study is completely voluntary. If you decide to participate in this study after you read this informed consent document, then

you must sign and date as evidence of your willingness to participate.

By signing this informed consent document, you are confirming the following:

- You understand what you have read.
- You consent to take part in this study.
- You consent to take the study treatment that is described.
- You consent to the use of use of your personal and health information as described in this document.

WHAT IS THE PURPOSE OF THE STUDY?

Many people suffer from irritable bowel syndrome (IBS) every year in the United States (US). The causes of IBS are complex and still not fully understood but may include imbalances in the gut flora or immune function, infections, dietary factors, and changes to gut permeability ("leaky gut"). Depending on the stool consistency, IBS can be classified as IBS with diarrhea (IBS-D), IBS with constipation (IBS- C), or mixed IBS (IBS-M). EBS Advanced IBS-D is an all-natural, plant-based nutritional supplement that contains a proprietary blend of amino acids that have been tested for use in patients undergoing radiation chemotherapy and has been available for purchase in the US since 2018.

It is an orally consumed beverage, which has been shown to reduce gastrointestinal permeability. Studies have shown that the proprietary blend of amino acids in EBS Advanced IBS-D can alleviate the symptoms associated with leaky gut and blunted villus that is caused by radiation chemotherapy. We are conducting this study to collect data about the tolerability of using EBS Advanced IBS-D in participants with IBS-D, as well as evaluate the potential benefits provided by daily consumption. The study will include a two-week period where you will record your IBS-D symptoms, followed by two weeks of daily study product usage and questionnaires. This study is being conducted by Protovate and will involve 120 adult participants.

This research study is for research purposes only. The only alternative is to not participate in this study.

WHY HAVE I BEEN INVITED AND AM I ELIGIBLE?

You have received this informed consent form because you have requested more information about the study. A member of the research team will confirm whether you are eligible.

You might be eligible to take part in the study if you:

- Are male or female aged 18-65
- Have Irritable Bowel Syndrome with diarrhea (IBS- D) (based on diagnosis by a doctor)

You are not eligible if you:

- Have been diagnosed with IBS-C, IBS-M, or IBS-U
- Have been diagnosed with gut abnormalities or disorders (for example, Crohn's disease, ulcerative colitis, celiac disorder)
- Expect to have changes made to long-term medications or plan to start new medication during the study period which is known to alter bowel function (for example, loperamide)
- Are allergic to any of the ingredients
- Are pregnant or breastfeeding

WHAT DOES TAKING PART IN THE STUDY INVOLVE?

Schedule and duration

This study will involve a Pre-screening period, a Run-in period, and an Observation Period. Each stage will be completed within the mobile application.

- Pre-Screening: Less than 60 minutes
- Run-in: Less than 15 minutes, every day for 2 weeks
- Observation Period: Consumption of beverage twice daily 30 minutes before a major meal and completing daily questionnaires (less than 15 minutes) for 2 weeks and on days 1 and 14, completing questionnaires which will take less than 60 minutes)

What happens during the study?

Eligible participants will be provided with enough bottles of the study product to consume for a 2-week period. You will be expected to consume the study product **on an empty stomach, 30 minutes prior to eating a major meal,** once in the morning and once in the evening.

You will be asked to complete daily **questionnaires** asking about your IBS-D symptoms, quality of life, work productivity, activity, and general health. You can opt-in to receive notifications to remind you to complete your daily questionnaire.

In addition, you will be asked to keep a daily **study diary** to record IBS-D symptoms and study product use. This will only involve answering a few questions. The diary will be available as an

online version that can be accessed on a mobile device. The research team will explain how to use it.

Procedures conducted at each appointment are described below.

Pre-screening

The research team will first discuss the study with you, and you will have an opportunity to ask questions before you decide if you want to proceed. If you decide to take part in the study, you will be asked to provide your written informed consent by electronically signing a consent form on the mobile application (the research team will instruct you through this). To do this, you should have either a touch screen smartphone, or tablet, or a computer/laptop.

Your medical history will be reviewed by the research team. If you meet the initial study eligibility criteria, you will be asked to partake in a 2-week run-in period. Data from your electronic diary will be reviewed after 14 days. If the data suggests that you are not suitable to proceed, you will receive an automated notification via email and text message to say you will not need to continue with the study. You can always contact the research team if you have any questions. If you do not meet the criteria to continue in the study at this stage, you will not be re-assessed.

Run-in period

Each day during the 2-week Run-in period, you will answer daily questions related to your IBS-D, including symptoms and lifestyle. At the end of this Run-in period, the research team will check your medical history, current medications, and your IBS-D symptoms to determine whether you are eligible to take part in the study. If you are confirmed to be eligible you will move on to the Observation period. you will receive additional study questionnaires (as described below in the Observation Period section), as well as EBS Advanced IBS-D study product, and will be explained how to use the study product for the next 2 weeks (see **What study product will I receive during the study?** Below).

Observation Period

The day you begin taking the study product, you will be asked to answer a series of questionnaires about your IBS-D symptoms, quality of life, work productivity, activity, and general health. During the 2-week observation period, you will record your daily IBS-D symptoms (including stool consistency, urgency, abdominal pain, cramping, and gas) via a mobile application, and provide additional information in your study diary about your experience with the study product. In addition, on the final day of the study product use, you will be asked to fill out the same series of questionnaires about your IBS-D symptoms, quality of life, work productivity, activity, and general health as you did at the beginning of

the Observation period.

What study product will I receive during the study?

If you are eligible to continue in the study after the 2- week Run-in period, you will receive the study product. The study is an open label study, which means that both the participants and the research team will know what the study product is and what it is comprised of. You will receive instructions on how to use the study product and will have the bottles of study product delivered to your home by a courier. You will be asked to provide consent to share your name, address, and phone number with the study contract research organization (Protovate) and study supplies warehouse which will arrange a courier delivery. They will aim to deliver the study product to you within 2 days.

The study product will be provided in 16-ounce bottles, each bottle containing two doses of EBS Advanced IBS-D. The study product is a liquid, with half of the bottles being Berry flavor and the other half being Valencia Orange flavor. 8 ounces of the study product will be consumed once in the morning on an empty stomach, prior to eating, with the other 8-ounces being consumed in the evening on an empty stomach, prior to eating. There will be a line on the bottle indicating the 8-ounce mark. You will receive up to 16 bottles for the 2-week observation period.

If you start running out of the study product at any point during the study, please contact the research team who will order additional supplies for you. After the 2-week EBS Advanced IBS-D observation period, you will no longer receive any study product as part of the study.

HOW CAN I TAKE PART?

If you are interested and wish to participate in the study, please begin the pre-screening procedure. The research team will reach out to you if you are eligible to begin the Run-in period of the study. Before enrolling you in the study, they will go through your IBS-D symptoms and medical history to confirm whether you are eligible to proceed to the 2-week observation period. The research team will discuss the study with you, and you will have an opportunity to ask questions before you decide if you want to proceed. If you decide to take part in the study, you will be asked to provide your signed informed consent and the research team will then send you information about pre-screening. After the 2-week Run-in period, the research team will confirm your eligibility to continue in the study.

For the research team to check your eligibility, you will need to provide a brief medical history, with a focus on your IBS-D diagnosis during the pre-screening stage. In addition, you will need to provide a list of medications that you would be taking during the study.

DO I HAVE TO TAKE PART?

No. It is up to you to decide if you want to take part in this study. Your participation in this study is completely voluntary. You may choose to not participate or you may withdraw from the study for any reason without penalty or loss of benefits to which you are otherwise entitled. If you decide not to take part, it will not affect your medical care.

If you decide to take part, you will be free to withdraw from the study at any time without providing a reason. This will not affect your medical care.

WHAT ARE THE POSSIBLE DISADVANTAGES OF TAKING PART AND THE SIDE EFFECTS OF THE STUDY PRODUCT?

EBS Advanced IBS-D is a plant-based beverage that contains amino acids, electrolytes, vitamins, minerals, and plant extracts. According to the manufacturer, there are no known side effects. Since the study product is investigational, there may be risks that are unknown. If you experience any serious side effects during the study, please contact your local research team immediately at the number listed on the first page of this form.

As part of this research, you may be required to use one or more of the following: a phone or web app/ site, an electronic study diary (eDiary), or a device that tracks information about you. While using these, information about you may be collected and shared with the researchers or people outside of the study. This data might include personal health information, location, call logs, text message history, web browsing history, or social media use. A complete description of the data collection and sharing for an app, eDiary, or device can commonly be found in the Terms of Use, End User License Agreement, or Privacy Policy associated with the device. If you would like to read these documents, request a copy or instructions about how to access this information from the Principal Investigator.

While the Terms of Use, End User License Agreement, or Privacy Policy may include statements limiting your rights if you are harmed as a result of your use of the app, eDiary, or device in this study, you do not release the Principal Investigator, sponsor, institution, or agents for responsibilities from mistakes. You also do not waive any of your rights as a research participant.

ARE THERE ANY BENEFITS FOR ME IN JOINING THE STUDY?

We cannot promise that the study will give you any direct benefit. However, your participation in the study can help us collect important information in order to improve treatments for IBS-D in the future.

IS THERE ANY REIMBURSEMENT FOR TAKING PART?

You will receive a $25 Walmart gift card for completing the pre-screening phase, a $75 Walmart gift card for the 2-week Run-in period, and if you are deemed eligible, you will receive a $75 Walmart gift card for completion of the 2-week Observation period as reimbursement for time spent.

COSTS

There will be no charge to you for your participation in this study. The study product will be provided at no charge to you or your insurance company.

WHAT HAPPENS WHEN THE STUDY STOPS?

When the study has finished, the sponsor of the study will analyze the results to look for any observed benefits of the study product. The sponsor may want to publish the results on their website or in medical journals. All results published will be anonymized, which means that you will not be able to be identified from them.

WHAT WILL HAPPEN IF I DON'T WANT TO CARRY ON WITH THE STUDY?

The study will be most valuable if few people withdraw from it, so it is important to discuss any concerns you may have with a member of the research team before you agree to participate. However, your participation in this study is completely voluntary and you can choose to withdraw at any point, without giving a reason. If you withdraw from the study, we will stop collecting information from you. However, data collected before your withdrawal can be used for the research. The Principal Investigator may stop the

study or you participation without your consent for a variety of reasons, which include but are not limited to:

- Participants experiencing adverse side effects.
- They study product showing evidence of not being effective.
- The study product not needing further investigation.
- Decisions made in the commercial interests of the sponsor.

NEW FINDINGS

Any new important information that is discovered during the study and which may influence your willingness to continue participation in the study will be provided to you.

WHOM TO CONTACT ABOUT THIS STUDY

During the study, if you experience any medical problems, suffer a research-related injury, or have questions, concerns or complaints about the study such as:

- Whom to contact in the case of a research-related injury or illness;
- Payment or compensation for being in the study, if any;
- Your responsibilities as a research participant;
- Eligibility to participate in the study;
- The Principal Investigator's or study site's decision to withdraw you from participation;
- Results of tests and/or procedures;

Please contact the Principal Investigator at the telephone number listed on the first page of this consent document.

If you seek emergency care, or hospitalization is required, alert the treating physician that you are participating in this research study.

An institutional review board (IRB) is an independent committee established to help protect the rights of research participants. If you have any questions about your rights as a research participant, contact:

- By **mail**:
    - Study Subject Adviser
    - Advarra IRB
    - 6100 Merriweather Dr., Suite 600
    - Columbia, MD 21044
- or call **toll free**:
- or by **email**:

Please reference the following number when contacting the Study Subject Adviser: Pro00065894.

ILLNESS OR INJURY AND COMPENSATION FOR INJURY

If you become ill or are injured because of your participation in the study, please immediately contact the research team (contact information provided on the first page of this form). They will provide you with any necessary information and will inform the study sponsor. In case of serious adverse reaction, contact your emergency services immediately at 9-1-1. If you are to become ill or get injured during the study, no compensation will be provided.

HOW WILL MY INFORMATION BE KEPT CONFIDENTIAL?

Entrinsic Bioscience, LLC. is the sponsor for this study based in the United States. They will be using information from you and/or your medical records in order to undertake this study and **will** act as the data controller for this study. This means that Entrinsic Bioscience LLC is responsible for looking after your information and using it properly, with your privacy being a priority. Entrinsic Bioscience LLC will not keep any identifiable information about you after the study has finished.

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways for the research to be reliable and accurate. If you withdraw from the study, the research team and the sponsor will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible. You can find out more about how Entrinsic Bioscience LLC uses your information by contacting the research team (contact information is in the section: **Study Details**).

The research site/clinic will collect information from you about your medical history for this study in accordance with our instructions. We will use your name and contact details to contact you about the study and make sure that relevant information about the study is recorded for your care, and oversee the quality of the study. Individuals from Entrinsic Bioscience LLC and regulatory organizations may look at your medical and research records to check the accuracy of the study. The research site/clinic will pass these details to Entrinsic Bioscience LLC along with the information collected from you and/or your reported medical history. The only people in Entrinsic Bioscience LLC, or third parties

contracted by Entrinsic Bioscience LLC, who will have access to information that identifies you, will be people who need to arrange or contact you regarding study treatment deliveries or audit the data collection process. The people who analyze the information will not be able to identify you and will not be able to find out your name, participant number, or contact details.

The research site/clinic will keep identifiable information about you from this study for 5 years after the study has finished. When you agree to take part in a study, information about your health and care may be provided to researchers running other research studies in this organization and other organizations. These organizations may be universities, organizations, or companies involved in health and care research in this country or abroad. This information will not identify you and will not be combined with other information in a way that could identify you. The information will only be used for the purpose of health and care research and cannot be used to contact you or to affect your care. It will not be used to make decisions about future services available to you, such as insurance.

WHO IS ORGANIZING AND FUNDING THE STUDY?

The study is organized by Protovate. The study is funded by Entrinsic Bioscience, LLC., which is the distributor of EBS Advanced IBS-D in the US, and is reviewed by the Internal Review Board, Advarra.

WHO HAS REVIEWED THIS STUDY?

This research has been reviewed by an independent group of people, called an Internal Review Board (IRB), which is there to protect your safety, rights, -well-being, and dignity. This study has been reviewed by the IRB, Advarra.

SOURCE FOR MORE INFORMATION

If you have any questions or queries or require any advice about any aspect of this study, please contact the research team whose details are provided above (in the section titled **WHOM TO CONTACT ABOUT THIS STUDY?**).

If you do not agree to all of the above statements, you should not sign and date this consent document.

Thank you for taking the time to read this Information Sheet.

CONSENT CONFIRMATION

I agree to the research participation agreement and acknowledge the research participation privacy notice.
I confirm that I am 18-65 years of age.
I have read this paper about the study or it was read to me.
I understand the possible risks and benefits of this study.
I understand and authorize the access, use and disclosure of my information as stated in this form.
I know that being in this study is voluntary.
I choose to be in this study: I will get a signed and dated copy of this consent form.

Participant's Name _____

Signature _____

Date _____

AUTHORIZATION TO USE AND DISCLOSE PROTECTED HEALTH INFORMATION

If you decide to be in this study, the Principal Investigator and research team will use and share health data about you to conduct the study. Health data may include:

- Your name.
- Address.
- Phone number.
- Date of birth.
- Medical history.

Health data may come from your study records or from existing records kept by your doctor or other health care workers.

For this study, the research team may share health data about you with authorized users. Authorized users may include:

- Representatives of Entrinsic Bioscience, LLC
- Representatives of Protovate
- Representatives of Advarra IRB (an Institutional Review Board that reviews this study).
- The Food and Drug Administration (FDA) and other US federal and state agencies.
- Government agencies to whom certain diseases (like HIV, hepatitis, and STDs) must be reported.
- Governmental agencies of other countries.
- Outside individuals and companies, such as laboratories and data storage companies, that work with the researchers and sponsor and need to access your information to conduct this study.
- Other research doctors and medical centers participating in this study, if applicable.
- A data safety monitoring board which oversees this study, if applicable.

Your health data will be used to conduct and oversee the research, including for instance:

- To see if the study product works and is safe.
- For other research activities related to the study product.

Once your health data has been shared with authorized users, it may no longer be protected by federal privacy law and could possibly be used or disclosed in ways other than those listed here.

Your permission to use and share health data about you will end in 50 years unless you revoke it (take it back) sooner.

You may revoke (take back) your permission to use and share health data about you at any time by writing to the Principal Investigator at the address listed on the first page of this form. If you do this, you will not be able to stay in this study. No new health data that identifies you will be gathered after your written request is received. However, health data about you that has already

been gathered may still be used and given to others as described in this form.

Your right to access your health data in the study records will be suspended during the study to keep from changing the study results. When the study is over, you can access your study health data.

If you decide not to sign this form, you will not be able to take part in the study.

STATEMENT OF AUTHORIZATION

I have read this form and its contents were explained. My questions have been answered. I voluntarily agree to allow research team to collect, use and share my health data as specified in this form. I will receive a signed and dated copy of this form for my records. I am not giving up any of my legal rights by signing this form.

_____
Printed Name of Participant

_____ _____
Signature of Participant Date