Institutional Review Board

Assent Document for Research Study

PI: Loren Denlinger, MD, PhD **Version Date: 01/25/2022**

Title of Study: PrecISE: Precision Interventions for Severe and/or Exacerbation-Prone Asthma Network **Version 4.0**

Institution/Hospital: University of Wisconsin – Madison

This assent document applies to 12-year old children.

Name of participant _____ Age_____

Below are the answers to some of the questions you may have. If you have any questions about what is written below or have any other questions about this research, please ask them. You will be given a copy of this consent form.

This assent will either be done in-person or remotely (by phone or video conference call). We will follow the same procedures and guidelines regardless of the method used to obtain your assent.

What is a research study?

Research studies help us learn new things. We can test new ideas. First, we ask a question. Then we try to find the answer. This paper talks about our research (called PrecISE) and the choice that you have to take part in it. You can ask questions any time.

Important things to know…

- You get to decide if you want to take part.
- No one will be upset if you say 'No'.
- If you say 'Yes', you can always say 'No' later.

Why are we doing this research?

We are doing this research to learn about new ways to treat severe asthma. One of the ways we are doing this is by using precision medicine. In precision medicine we try to figure out what treatments are best for certain patients based on some of their characteristics; we call these characteristics *biomarkers*. Biomarkers are bits of information about you. We will collect these biomarkers in PrecISE using different tests, including blood tests and studying your breath.

What would happen if I join this research?

In PrecISE we are studying different treatments for severe asthma. You are being asked to join because you have been diagnosed with severe asthma. If you choose to take part in the study, you will receive between 1-3 different treatments. Right now the study is starting with two treatments. The table below shows the current treatment available, and we will talk more about it at the end of this form. If new treatments are added to the study later on, we will give you information about them at that time and will ask you to consent to receiving them. When you turn 18 you will have a choice to receive information about our study treatments available for adults and consent to receiving them. Your total time in the study will be at least 14 months.

Possible treatments:

Treatment	Brief Description
medium chain triglyceride (MCT)	Food Supplement, powder, similar to protein powder, that can be mixed with food or water
Broncho-Vaxom	Drug given as oral capsules

If you are eligible (qualified) for the study, you will be randomly assigned to either the MCT active treatment, the MCT placebo, the Broncho-Vaxom active treatment or the Broncho-Vaxom placebo. **Random assignment** is like rolling a dice to assign you either the active or placebo. A **placebo** looks like the treatment but doesn't contain active ingredients (like a sugar pill).

The things you will do on this study are listed below, and you can find more information on the different visits in the *Schedule of Study Visits* at the end of this document. During the first 1-4 study visits, we will make sure you are eligible for the study. If you qualify, you will begin treatment visits. This is where we randomly assign you to a treatment and give you the treatment to take home. These visits will be once a month for 4 months. You will take a 2 to 4 month break before starting another treatment, but we will ask you to come in for visits during this time. Most visits will be between 2-4 hours. The study activities will be conducted during visits to the clinic, but some things, such as spirometry may also be done at home. Due to the COVID-19 pandemic, not all procedures will be done at all clinic visits.

Study visits will be completed at the UW-Madison University Hospital.

Study Activities:

Consent: You will review and sign this assent form, if you agree to participate. Your parent or guardian will review and sign the parent permission form, if they give permission for you to participate.

Eligibility: We will make sure you qualify for the study at the beginning then will continue to make sure you still qualify all through the study.

Physical Exam: You will receive an exam to see how healthy you are. We will look at your health, skin, eyes, ear/nose/throat, heart, chest, abdomen, arms and legs. Your blood pressure, heart rate, breathing rate, and temperature will be taken.

Questionnaires: With your parent or guardian's help, we will ask you to both read questions on a computer and to answer questions from a study coordinator (people helping us with this study).

Pulmonary Function Testing: These are tests that show how well your lungs are working

- *Spirometry:* This will test how well your lungs work by measuring how much air you inhale, how much you exhale and how quickly you exhale.
- *Holding off on your medications:* Before you do the spirometry, you will be asked to briefly stop taking some of the medications you currently take for your asthma, however, even though the test works better if you follow the instructions, you should take your medications if you need to.
- *Maximum Bronchodilator Response Test:* During this test, you will take puffs of albuterol (this is used to treat asthma) to open your airways then do spirometry again to test how well your lungs work. These two things (puffs of albuterol and then spirometry) may be repeated more than once.
- *Methacholine Challenge (if necessary)*: The methacholine challenge will be used to measure your asthma status if the maximum bronchodilator response test cannot tell us this information. Methacholine is a chemical that can cause the airway tubes to tighten and can bring on asthma symptoms. During the test, you will be asked to inhale low amounts of methacholine. These amounts will slowly be increased so that we can monitor you. A breathing test will be done after each time you take methacholine in order to measure your airways. We will monitor you closely and give you medication, if needed.

Safety Labs: Different tests will be done to ensure your safety, including:

- If you have had your first menstrual cycle we will test your urine for pregnancy. This will be done throughout the study. We ask you to do this because there is not enough information about the treatments we are testing to be absolutely sure that they are safe for a growing baby. A positive pregnancy test will be disclosed to you and your parent/guardian unless disclosure is prohibited by local regulations. It may not be possible to keep the results of pregnancy testing confidential. You will not be enrolled if you are pregnant or breastfeeding. If you become pregnant during the study, we will ask that you let us know. If you are a female who can get pregnant you will need to use regular and highly effective birth control while in this study.
- Blood and urine will be taken to make sure you're healthy.
    - Please see Table 3 in the Master Consent part 1 for information on the amount of blood we will collect.
    - Your parent or guardian will be informed of test results that are not normal so that you can follow-up

with your doctor.
- The blood and urine will also be used to help us figure out your biomarkers.

Measuring Asthma symptoms at home: You will be given a device to use at home during your participation in the study. This device will be used to check on how you are using your controller and rescue medications. You will also be given a device called a home spirometer to check on your asthma at home.

You may also be asked to complete a paper or online survey twice a day to answer some questions about your asthma. The online survey will be on a website called Qualtrics. If you are asked to complete questions using a Qualtrics survey, you will receive the survey link in a text message.

Please indicate your response below:

I understand that I may receive text messages from Qualtrics twice a day in order to complete questions about my asthma.

_____
Participant's Initials

Controller and Rescue Medication: As part of this study, you can receive asthma controller and rescue medication if you choose to. The controller medication we will offer will be the Advair Diskus inhaler and the rescue medication will be Ventolin (albuterol sulfate). The study coordinator will go over how you use these and will answer questions. You will be asked to bring back these inhalers to each visit, even if they are empty, and you will receive more if you choose to continue using them. It is important that you adhere to your controller medication throughout the study.

Do you agree to receive the optional, study supplied, controller medication (Advair Diskus)?

Circle one: Yes No _____
Participant's Initials

Do you agree to receive the optional, study supplied, rescue medication (Ventolin)?

Circle one: Yes No _____
Participant's Initials

Lifestyle Considerations: In order to qualify for the study, we will ask that you do the following, throughout the duration of the study:
- Do not use tobacco products and nicotine containing products (including e-cigarettes, patches).
- Do not use inhaled marijuana.
- Do not use any illegal drugs including abuse of prescription drugs.
- *For females who can become pregnant:* you must use a highly effective form of birth control. This is described in more detail in the *Parent Permission Form.*
- Males, who are sexually active with a female who can get pregnant, must agree to use a medically acceptable form of birth control, such as barrier protection, as determined by the study doctor.

- Contraception should be used for at least 1 month prior to screening, throughout study participation and for an additional 16 weeks after the end of the final test treatment.

Biomarkers: We will collect your unique characteristics (biomarkers) by blood, urine, and by a breathing test called fractional exhaled nitric oxide (FeNO)

- Please see Table 3 in the Master Consent part 1 for information on the amount of blood we will collect.
- A sample of urine will be collected.
- For FeNO, you will gently blow air out into a machine for 10 seconds so that the study team can measure the amount of nitric oxide in your breath. Nitric oxide helps us test your asthma.

Nasal swab: We will collect samples from inside your nose.

Induced Sputum: To do this test, we will need to get mucus (phlegm) from your airways. This will allow us to test samples from inside your body. You will be asked to breathe in a salty mist for up to 12 minutes and to cough deeply and vigorously every two minutes in order to bring up a sample of sputum (mucus) from your lungs.

CT Scan: The CT scanner uses x-rays to make pictures. You will be asked to lie on a table with your arms resting above your head. You will need to remain still and hold your breath for about 10-20 seconds during each scan. You will then be asked to breathe out and hold your breath again and the scan will be repeated. If you are a female who can get pregnant, you will have a pregnancy test to make sure that you are not pregnant before having the CT scan. The maximum amount of radiation you will be exposed to from the 2 CT scans during this study is between 3-9mSv. Another way of understanding this is to compare the exposure from the CT scans to the radiation exposure you receive from natural sources. The maximum radiation exposure from the 2 CT scans is equal to the amount of natural background radiation that the average person in the United States receives in about 1 to 2 years.

Do you agree to receive a CT scan? Circle one: Yes No _____ Participant's Initials

Randomization: You will be randomized to *Medium Chain Triglycerides (MCT)*, *Broncho-Vaxom*, or their placebos. You and the study staff will not know whether you are receiving active treatment or placebo.

Dispense Study Treatment: During the first 4 treatment visits, you will receive study treatment. MCT will come as packets of powder in a box. Broncho-Vaxom will come in blisters in a box.

Do I have to be in this research study and can I stop if I want to?

Taking part in this research study is completely voluntary. You may choose not to take part at all or stop participating at any time. If you decide not to be in this study, or if you stop participating at any time, no one will be mad at you.

Could bad things happen if I join this research?

We will try to make sure that no bad things happen. Some of the tests can make you feel uncomfortable. For example, taking your blood can hurt and sometimes the needle can leave a bruise on your skin. During other tests you might feel dizzy, nauseous or short of breath or you might get a headache. You can say 'no' to what we ask you to do for the research at any time and we will stop.

Could it make me sick [or sicker]?

Some people who take MCT (the first treatment) experience stomach aches, diarrhea, vomiting, nausea, and gas. If you tell us that you are experiencing these side effects, we will change the amount of treatment you are taking to try and make you feel better.

Will anyone know that I am in this research study?

Protecting your privacy is a top priority for PrecISE. To make sure the information we collect about you is private, we will assign a code number to you. We will use this code number on the documents with your medical information and will keep your name separate from this information. Only people who are authorized can view these files.

How will this research help me or other people?

We think being in this research may help you because it is possible that the treatments we are studying will help people with severe asthma. If we learn that they do, they may also help other people in the future.

Will you get any money or gifts for being in this research study?

You will get money for your participation in PrecISE. The amount you receive depends on which parts of the study you complete. If you stop participating before the end of the study or if the study is discontinued through no fault of yours, you will receive a partial payment based upon your participation in the study.

We ask you to do certain study tasks at home twice a day, every day during the study. We will pay you extra at each visit based on how often you completed these home tasks. This is called a compliance bonus. If you complete your daily study tasks most of the time you will earn the full bonus ($50 per visit). If you complete your daily study tasks some of the time, you will earn $25/visit. You will not get any bonus if you complete your daily study tasks less than half of the time. You should talk with your parents about how you would like to use the money you earn in the study.

At longer visits, you may also receive vouchers for food in the UWHC Cafeteria. Additionally, if you (or your parent) don't own a device that meets the requirements for this study, we can lend you a device for the duration of the study. You must return the device at the end of the study. More details are in the Master Consent, Part 2.

What else should I know about this research?

If you don't want to be in the study, you don't have to be. It is also OK to say yes and change your mind later. You can stop being in the research at any time. If you want to stop, please tell the research doctors.

You can ask questions any time. You can talk to any of the study coordinators or study doctors. Ask us any questions you have. Take the time you need to make your choice.

Can I do something else instead of this research?

Your other choices include getting regular treatments from your doctor for your severe asthma without being in a study. There may also be other studies that you could participate in. You and your doctor can decide on the best treatment for you.

What happens when I turn 18?

We will ask you to sign an adult consent.

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Schedule of Study Visits***:

Study Visit:	Screening	Run-in	V1	V2	V3	V4	V5	V6
	1-3 Visits		Can occur multiple times					
Timing: (week number)	-8 to -10	-4	0	4	8	12	16	20
What happens /What you need to do:								
Your study doctor or coordinator will check that you are suitable to take part in the study	X	X						
Your study doctor or coordinator will perform a physical exam	X	X	X	X	X	X	X	X
Your study doctor or coordinator will dispense more controller medication to you, if you choose to receive it	X	X	X	X	X	X	X	X
You will be randomized to a treatment or placebo			X					
You will get study drug			X	X	X	X		
You will fill out surveys on your medical, asthma and allergy history****	X							
You will fill out surveys about how you are feeling, and about any other medicines you are taking****	X	X	X	X	X	X	X	X
You will fill out surveys about your household****	X							
You will go through Pulmonary Function Testing**	X	X	X	X	X	X	X	X
Blood and Urine will be taken for Safety Tests*****	X	X	X		X		X	X
Biospecimens (blood, urine, sputum) will be taken to determine your biomarkers and to assess your progress			X		X		X	X
You will be asked to have an CT scan		X						
You will be asked to produce a sputum sample		X						

**Pulmonary function tests may be conducted in the home in addition to in the clinic at the Screening, Run-In, V1 and V6 visits.
*** Please note that it is possible that some procedures could be performed at time points that are different than what is noted in the table.
****These could be done in-person or remotely.
*****Safety tests will either be conducted in clinic or at patient services centers (ex. LabCorp)

TREATMENT INFORMATION DOCUMENT - MEDIUM CHAIN TRIGLYCERIDES (MCT)

Information about the treatment:

Medium chain triglycerides (MCT) is something you add to your food. It that has nutrients thought to help severe asthma.

How will I take the treatment?

The treatment will come in packets of powder that you can mix in different foods and drinks. It is best to take the treatment before or with meals. We will let you know how many packets you need to take.

Are there special things I'll need to do while I'm on this treatment?

You'll let us know about the foods you have eaten, any side effects you've experiences and we'll check your urine and blood to monitor your safety.

Are there risks of this treatment?

Most people can take MCT without many problems.

Risks include:

Likely: Stomach aches
Less Likely: Diarrhea, vomiting, irritability, nausea and gas
Rare: Urgent need to pass a bowel movement, severe short-term diarrhea and dehydration

What are possible benefits?

Studies suggest MCT might be good for your heart. MCT could help make you feel full which would decrease the amount of food you eat.

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TREATMENT INFORMATION DOCUMENT - BRONCHO-VAXOM

Information about the treatment:
Broncho-Vaxom is an oral medication thought to improve asthma control by the reduction of asthma exacerbations and respiratory infections in affected patients. Broncho-Vaxom has been shown to potentially modify the gut microbiome, which leads to regulating airway inflammation in animal models of asthma.

How will the treatment be administered?
The treatment will come in capsules and should be consumed in the morning on an empty stomach. The capsules (2 x 3.5mg once daily) can be swallowed with water or the contents mixed with beverages. Participants will consume the Broncho-Vaxom capsules daily for the 4-month treatment period.

Are there treatment specific procedures?
During treatment visits, participants will perform the study-related procedures and provide stool samples to monitor biological markers.

What are the risks of this treatment?
Broncho-Vaxom is well tolerated by most people.
Risks include:
Possible: Diarrhea or headache
Less Likely: Abdominal pain, nausea, vomiting, a skin rash accompanying a disease or fever, hives, difficult or labored breathing, cough, asthma, and tiredness.
Rare: Fever and allergic reactions.

What are possible benefits?
Broncho-Vaxom studies have shown to improve symptoms in adult patients with chronic obstructive pulmonary disease (COPD). Oral lyophilized extracts of bacteria have been shown to prevent moderate and severe asthma exacerbations in children aged 6-16 years.

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CONTROLLER MEDICATION INFORMATION DOCUMENT – ADVAIR DISKUS

Information about the medication:
A controller medication is medicine that works over a period of time to ease inflammation in your airways and help prevent asthma symptoms.

How will the drug be administered?
It will be administered via an inhaler.

What are possible side effects of Advair Diskus?

- upper respiratory tract infections
- headaches
- dizziness
- nausea
- vomiting
- stomach upset
- diarrhea
- yeast infections of the mouth or throat (oral thrush)
- sore throat
- dry mouth/nose/throat
- stuffy nose
- sinus pain
- cough
- sore throat
- hoarseness or deepened voice
- musculoskeletal pain

What Drugs, Substances, or Supplements Interact with Advair Diskus?
Advair Diskus may interact with amiodarone, diuretics (water pills), HIV medicines, MAO inhibitors, antidepressants, antibiotics, antifungal medications, or beta-blockers. Tell your doctor all medications and supplements you use.

RESCUE MEDICATION INFORMATION DOCUMENT – VENTOLIN

Information about the medication:
A rescue medicine is a fast-acting medicine that works immediately to relieve asthma symptoms when they happen.

How will the drug be administered?
It will be administered via an inhaler.

What are possible side effects of Ventolin HFA?

- worsening trouble breathing, coughing, and wheezing (paradoxical bronchospasm). If this happens, stop using Ventolin HFA and call your healthcare provider or get emergency help right away. This is more likely to happen with your first use of a new canister of medicine
- heart problems, including faster heart rate and higher blood pressure
- possible death in people with asthma who use too much Ventolin HFA
- serious allergic reactions. Call your healthcare provider or get emergency medical care if you get any of the following symptoms of a serious allergic reaction:
  - rash
  - hives
  - swelling of your face, mouth, and tongue
  - breathing problems
  - changes in laboratory blood values (sugar, potassium).
- Common side effects of Ventolin HFA include:
  - sore throat
  - upper respiratory tract infection, including viral infection
  - cough
  - muscle pain
  - your heart feels like it is pounding or racing (palpitations)
  - chest pain
  - fast heart rate
  - shakiness
  - nervousness
  - dizziness

Get medical help right away if Ventolin HFA no longer helps your symptoms (like wheezing and trouble breathing), if your symptoms get worse, or if you need to use your inhaler more often.

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NEW TREATMENTS

This study involves multiple potential treatments. Detailed information about these treatments is included below. If new treatments are added to the study later on, you will be asked to review information about the new treatments and consent to those separately. **If you choose not to consent to the new treatments when they are added to the study, your participation with the current treatments will not be affected.**

Please indicate your response below:

NEW PARTICIPANTS ONLY
I agree to all treatments currently approved for PrecISE (medium chain triglycerides (MCT) and Broncho-Vaxom).

Circle one: **Yes** **No** _____
Participant's Initials

CURRENT PARTICIPANTS ONLY
I agree to receive Broncho-Vaxom. I understand that if I do not agree to receive Broncho-Vaxom, then I will continue in the study on MCT.

Circle one: **Yes** **No** _____
Participant's Initials

Is there anything else?

If you want to be in the research after we talk, please write your name below. This shows we talked about the research and that you want to take part.

Name of Participant: _____
(To be written by child/adolescent)

Consent Obtained by: _____
Signature Printed Name and Title

_____ _____
Date Time