CONSENT FORM: CYSTIC FIBROSIS PARTICIPANTS
The Impact of Insulin Therapy on Protein Turnover in Pre-Diabetic Cystic Fibrosis Patients

You are invited to participate in a research study that will help us determine if low-dose insulin replacement therapy will help prevent protein breakdown in CF patients who have abnormal or indeterminate glucose tolerance. You were selected as a possible participant because you have CF and a routine oral glucose tolerance test has shown abnormal or indeterminate glucose tolerance. We ask that you read this form and ask any questions you may have before agreeing to be in the study. This study is being conducted at the University of Minnesota by Dr. Toni Moran and at Children's Hospitals and Clinics of Minnesota by Dr. Laura Gandrud. Dr. Sree Nair at the Mayo Clinic is a collaborator who will be doing the tests on the blood samples.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

Study Purpose
Abnormal or indeterminate glucose tolerance, which is detected by the oral glucose tolerance test, is very common in CF because damage to the pancreas causes insulin deficiency. Low levels of insulin lead to higher blood glucose levels, and can eventually progress to diabetes. One of our main concerns in CF is that the low levels of insulin can also lead to abnormal protein breakdown, even when the blood sugar levels are normal. This makes it difficult to maintain a good muscle mass, which we know is important for lung function. The purpose of this study is to determine if replacing insulin deficiency with low dose insulin therapy reduces protein breakdown.

Study Procedures
If you agree to participate in this study, we will ask you to do the following over 8 weeks:

<u>Phase 1 (2 weeks)</u>

a) First we will measure your current level of protein breakdown. We will do this over a period of 2 weeks. You will spend the first day in the research unit at the University of Minnesota to do a "**jello study**". This part of the study will take place early in the morning until mid- to late afternoon. You will need to have fasted (except water) for 10 hours. Two intravenous catheters (small plastic tubes called IVs) will be placed. One will be used to deliver amino acids (the building blocks of protein), and the other to take blood samples (like a faucet, so we don't have to repeatedly poke you).

   Amino acids are present naturally in our bodies where they occur in various forms, called isotopes, that just differ by an atom or two. Some isotopes are much more common in the body than others. We will give you stable isotopes---these are not radioactive or harmful, they are simply the less common isotopes. We can measure these in the blood, and this helps us determine how the body breaks down and builds protein. We will also look at measures of inflammation since this can affect protein breakdown.

We will deliver these amino acids by IV for 8 hours. After the first 3 hours we will feed you jello that has been specially prepared so that the protein in it also has stable amino acids. Because some people have felt nauseated after consuming the jello on an empty stomach, we will give a dose of the anti-nausea drug Zofran before the jello. We will take blood samples until 5 hours after you have consumed the jello. We will take about 5 ounces (10 tablespoons) of blood, an amount your body can easily replace. Once you have completed the "jello study", we will remove the IVs and feed you a regular meal and send you home.

DXA Scan: Either at the end of the study or the beginning we will perform a DXA scan. DXA is usually used to measure bone mineral density, but in this case it will be used to tell us your body composition (how much is made of muscle because we need this for our calculations).

b) At the time of the jello study we will set you up with a continuous glucose monitor. This is a device commonly worn by people with diabetes to give a continuous reading of blood sugar levels. A very small needle is inserted in the skin of the abdomen or buttocks. It is attached to a flat disc approximately 1 inch in diameter which is the sensor. This is taped to the skin. You are able to shower and perform all usual aspects of daily living while wearing the sensor. We will take it off when you return a week later for the blood draw.

c) We will have you complete 2 surveys during your jello visits. One of the surveys is the CFQ-R, which inquires about your quality of life with CF. The other survey asks about your perceptions on insulin use before you use any insulin. You will then retake both surveys at the 6 week jello visit after a month of insulin use.

d) We will have you keep diet records for 3 days after the jello study so we can estimate how much protein is in the diet and how many calories per day you eat.

e) We will look at your medical records to determine lung function over the previous year.

f) We will ask you questions about your health and perform a routine physical examination. This is to be sure that you do not have any health problems that would prevent you from being in the study.

g) You will complete a urine pregnancy test, for those that are of child bearing potential. Though there is be no harm to the fetus if you are pregnant, your results from the study would be skewed.

h) After the jello study, you will be asked to come back for two fasting blood draws, one a week later, the other 2 weeks later. Each will take 1 tsp of blood. The blood draws will help us measure protein breakdown. Each of these visits will last about 30 minutes. You will then be ready to enter phase 2.

If at any point during Phase 1 you become ill, we may ask you to repeat the study after 6 weeks' time.

Phase 2 (6 weeks)

a) Phase 2 will look at whether insulin reduces protein breakdown. Two out of three subjects will

be started on low-dose insulin and one out of three on placebo:

- 1/3 of subjects will be started on once daily insulin, a long-acting background insulin.
- 1/3 of subjects will be started on short-acting pre-meal insulin, three times per day.

1/3 of subjects will get placebo (half of them once a day, half three times a day). The placebo consists of the solution that insulin is made in, but without the insulin (it is called insulin diluent). It is important to have a placebo group so that we know if the insulin really makes a difference

b) You will take study drug for a total of 6 weeks. After the first 4 weeks, you will come to the research center to repeat the jello study and the DXA scan. As in Phase 1, you will have blood draws one week later and 2 weeks later to assess protein breakdown. After this last blood draw you will stop study drug and the study will be over.

c) As in Phase 1, we will set you up with a continuous glucose monitor for one week, and do 3 days of diet records after the jello study.

d) In addition, while you are on study drug, we will ask you to check blood glucose levels at home. We will give you a finger-poker and a glucose monitor to do this. A "glucose profile" means 3 glucose levels in one day---first thing in the morning before eating, right before the main meal, and 2 hours after the main meal. We will ask you to do this at least once a week, and more while we are adjusting the insulin dose.

If at any point during Phase 2 you become ill, we may ask you to repeat that phase of the study after 6 weeks' time.

Contact with study personnel

a) You will have a total of 2 visits to the UMN research center for jello studies, and 4 quick visits for blood draws over 8 weeks.

b) We will provide you with basic CF related diabetes education at the time of each jello study.

c) Study personnel will be in contact with you (telephone, email) weekly during the study.

Risks of Study Participation

The study has the following risks:

1. There is a potential for low blood sugars if you are on too much insulin or from fasting for a long period of time. Mild low blood sugars feel uncomfortable (hot, sweaty, hungry, rapid heart rate). More severe low blood sugars can make a person confused and even lead to unconsciousness. We will be giving you a very low dose of insulin and will be monitoring you during the entire Jello part of the study and do not anticipate that this will be a problem. However, we will teach you to recognize signs of low blood sugar and how to treat it with carbohydrate-containing food or beverage. We will adjust the insulin dose if necessary to prevent this. During the Jello test, we will give you some juice if you are feeling symptomatic.
2. This study will require you have 2 intravenous tubes (IVs) placed for blood drawing and for giving you the proteins. You may have some restriction of movement while the IV is in place. You may have temporary pain and bleeding or bruising at the site where the IV enters the skin.

In about 1 in 10 cases, a small amount of bleeding under the skin will produce a bruise. The IV site could get infected but this does not happen very often. Some people have reported some skin irritation or pain at the IV site. Experienced personnel will insert the IVs to minimize this risk.

3. The stable isotopes to be infused are naturally occurring isotopes of amino acids and thus are not anticipated to pose any risk. The infusions will be prepared by the investigational pharmacy to ensure they are sterile.
4. Less than 10% of people have experienced nausea eating the jello on an empty stomach. Because the jello is very expensive and we want to make sure you can consume all of it, we will give Zofran, an anti-nausea drug before the jello meal.
5. Zofran is a drug commonly given to treat nausea after chemotherapy or surgery. It is generally very well tolerated. One out of 10 people receiving this drug experience headache and 1 out of 25 experience constipation. Less than 1 out of 100 people experience warmth or flushing. There have been rare reports of more serious problems. We are giving the lowest dose (4 mg), and only giving it once. In contrast, people taking this drug during chemotherapy may take up to 24 mg per day.
6. DXA is a form of ionizing radiation (like an x-ray). The DXA is for research only and not part of your medical care. DXA has very little radiation exposure---even with the two DXAs you will have in this study (1 with each Jello study), it is less than one gets just from the atmosphere living in Minnesota for 1 week. This exposure involves minimal risk and is necessary to obtain the research information. If you are of child bearing potential, you will have to complete a urine pregnancy test best completing the DXA scans.
7. You will be asked to complete the two surveys at both the jello visits. Some of the questions ask about your private attitudes, feelings, and behaviors related to insulin use and your CF. You can refuse to answer any questions that make you feel uncomfortable and you may take a break, decide not to answer questions, or stop taking part in the study at any time. Many precautions will be make to keep your information confidential, but this is not a guarantee. Your responses will be kept in a secure location with the study staff. Risks may include: psychological stress and/or loss of confidentiality.

Benefits of Study Participation

There is no direct benefit to you other than the knowledge that you are helping with scientific research that may someday help someone else.

Study Costs/Compensation

This study will not cost you anything. To compensate for the time spent, you will receive $140 for each infusion, and $15 for each of the additional blood draws. At the end of the study you will receive a $60 bonus if you complete the entire study, for a possible total of $400. If you need to repeat any study visits, you will be compensated accordingly.

Research Related Injury

In the event that this research activity results in an injury, treatment will be available, including first aid, emergency treatment and follow-up care as needed. Care for such injuries will be billed in the ordinary manner to you or your insurance company. If you think that you have suffered a research related injury, let the study physicians know right away.

Confidentiality

Your records will be kept private. Dr. Moran will keep the study data and your name on her password-protected desktop computer kept in her secure UM office. No one outside of Dr. Moran and the research team will have access to your name or identifying information. All samples sent to the Mayo Clinic will not have any information from which you could be identified. In any publications or presentations, we will not include any information that will make it possible to identify you as a subject. Your record for the study may, however, be reviewed by departments at

the University with appropriate regulatory oversight. To these extents, confidentiality is not absolute.

Protected Health Information (PHI)

We are committed to respect your privacy and to keep your personal information confidential. When choosing to take part in this study, you are giving us the permission to use your personal health information that includes 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. Those persons who get your health information may not be required by Federal privacy laws (such as the 1099 Rule) to protect it. Some of those persons may be able to share your information with others without your separate permission. Please read the HIPAA Authorization form that we have provided and discussed. The results of this study may also be used for teaching, publications, or for presentation at scientific meetings.

Voluntary Nature of the Study

Participation in this study is voluntary. Your decision whether or not to participate in this study will not affect your current or future relations with the University. If you decide to participate, you are free to withdraw at any time without affecting those relationships.

Study Results

After all subjects have completed the study and the results are analyzed, we will let you know the overall study results and whether you received insulin or placebo.

Contacts and Questions

The researcher conducting this study at UMN is Dr. Toni Moran. You may ask any questions you have now, or if you have questions later, **you are encouraged to** contact her at 612-624-5409 (email moran001@umn.edu).

This research has been reviewed and approved by an Institutional Review Board (IRB) within the Human Research Protections Program (HRPP). To share feedback privately with the HRPP about your research experience, call the Research Participants' Advocate Line at 612-625- 1650 or go to https://research.umn.edu/units/hrpp/research-participants/questions- concerns. You are encouraged to contact the HRPP 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 participant.
- You want to get information or provide input about this research.

You will be given a copy of this form to keep for your records.

Statement of Consent for the Study

I have read the above information. I have asked questions and have received answers. I consent to participate in the study.

Printed Name: _____

Signature of Participant: _____

Date: _____

Signature of Person Obtaining Consent: _____

Printed Name of Person Obtaining Consent: _____

Date: _____