Informed Consent: Randomized Trial

Title of Research Project:	**Nutrition and Exercise in Critical Illness (The NEXIS Trial): A Randomized Trial of Combined Cycle Ergometry and Amino Acids in the ICU**
Funder:	**The National Institutes of Health (NIH), Baxter International Inc., EnableMe**
NCT ID (ClinicalTrials.gov):	**03021902**
Principal Investigator:	**Renee Stapleton, MD, PhD**
Participant Name:	_____

We encourage you to ask questions and take the opportunity to discuss the study with anyone who you think can help you make this decision. You will be given a copy of this form to keep as a record.

Throughout this form 'you' refers to yourself or to the person for whom you are acting as the legally authorized representative.

You are being invited to participate in a clinical trial (a type of study that involves research). Many of the current treatments available to you are available because previous patients like you participated in clinical trials, and future advances in therapies are dependent on participation in clinical trials. You are being invited to take part in this research study because you are critically ill and have acute respiratory failure (ARF). The purpose of this study is to learn if giving a patient with ARF a combination of protein supplementation and in-bed cycle exercise will help in their recovery from their illness. It is our hope that these two treatments together will improve physical functioning, reduce or prevent muscle wasting and improve health-related quality of life for our patients. This study is being conducted by the University of Vermont at the UVM Medical Center.

The study is paid for by a research grant from the National Institutes of Health. Baxter, the company that makes the amino acids, is providing the amino acids for the study as well as some funding to support research pharmacy activities. EnableMe, the American distributor of the in-bed cycle ergometer (manufactured by Reck), is providing each participating hospital with a cycle for use during the study.

Why is This Research Study Being Conducted?

More than 750,000 Americans suffer from ARF every year. With recent improvements in treatments, more ARF patients are surviving their illness, but these survivors often experience health problems long after they leave the hospital, including muscle weakness and reduced physical functioning. Some earlier studies have shown that ARF patients receiving optimal amounts of protein may have fewer infections, spend less time on the mechanical ventilator (i.e. breathing machine), spend less time in the hospital, and may reduce deaths. Some ICU-based exercise studies in ARF have found patients spend less time on the ventilator (i.e. breathing machine), less time in the ICU, and have improved muscle strength and physical functioning.

How Many People Will Take Part In The Study?

A total of 142 patients will be recruited from approximately 4 medical centers in the US to take part in the study. We expect to enroll approximately 35 patients at the University of Vermont Medical Center.

What Is Involved In The Study?

Patients who enter the study will be assigned to one of two treatment plans (Plan A or Plan B). You will not be able to choose which treatment you receive. The treatment plan offered to you will be picked by chance, like the tossing of a coin. The chances of receiving either of the treatments are equal. You will receive the assigned study treatment plan until you are transferred out of the ICU or for 21 days, whichever occurs first. If you are transferred out of the ICU and later return to the ICU before you are discharged from the hospital, you will be in the same study group and the study procedures will start up again.

Treatment Plan A	ICU usual care ***and*** a combination of amino acid supplement (the building blocks for proteins) and cycle ergometry (stationary bike) exercise intervention.
Treatment Plan B	ICU usual care

Patients in Treatment Plan A:

- The ***amino acid supplement*** will be given continuously through an intravenous line (IV) that is already in place for your clinical care for 5 out of 7 days each week. Since it is possible that you may be already receiving protein as part of your prescribed nutrition while in the hospital, the dose of the study amino acid supplement will be monitored and adjusted up or down to make sure you receive the correct total amount each day.
- ***Exercise*** (stationary bike) sessions will occur once a day, for 5 out of 7 days each week. At the start of each session, your legs will be comfortably secured within the cradles that are attached to the pedals of the in-bed bike. Each session will be up to 45 minutes long. During each session you will be monitored for comfort and safety and verbally encouraged to actively cycle. If you are able to actively cycle, the cycling may gradually become more difficult during each session as long as you can tolerate it well.

Patients in Treatment Plan B:

- Will receive usual care protein
- Will receive usual care exercise

For all patients (Plan A and B):

- Before treatment is started, some information about your medical condition will be collected from the information already available in your medical record.
- A urine pregnancy test will be done before starting the study, if relevant.
- In most cases, all the tests needed to determine if a patient qualifies to take part in the study will have already been done as part of their routine ICU care. We will use results of these tests to determine if a patient is eligible for the study.
- We will perform several measures during the study.
    - Physical functioning will be tested by seeing how far you can walk in 6 minutes when you are discharged from the hospital.
    - A physician will examine you to determine the overall strength of your upper body and lower body.
    - We will use a hand-held tool to test your grip strength and the muscle strength of your upper legs.
    - An ultrasound will be done on your upper legs today, when you leave the ICU, and when you are discharged from the hospital.

- If a CT scan of your chest and/or abdomen is done for clinical reasons while you are in the hospital, we will look at the images to determine if you have lost any body mass or muscle. We will not be ordering or obtaining any CT scans as part of the study.
- If we are not able to do these tests before you are discharged from the hospital, we may ask to follow up with you within 7 days of your hospital discharge to perform these tests

Approximately 3 months after you are discharged from the hospital, a study coordinator will call you and confirm your contact information. The coordinator will call you again approximately 3 months later (about 6 months after you started the study) and ask you several questions about your physical functioning, the activities you are able to do, the state of your health, whether you have returned to work and/or your usual activities, and to see if you have been admitted to a hospital, rehabilitation center, or nursing home since your discharge. This call will take about 30 minutes.

What Are The Risks and Discomforts Of The Study?

Both the amino acid and cycling interventions are very safe. Amino acid supplementation may be harmful in patients with advanced liver disease because it can cause extreme sleepiness, so these patients are not eligible to participate in the study. Uremia (a high blood concentration of urea) can occur in patients with kidney failure. High urea has not been shown to be toxic, but patients with moderate to severe acute kidney injury will have their urea level monitored and if it is elevated we will reduce the dose of amino acids in half as a safety precaution.

In-bed cycling is also very safe. The potential risks of in-bed cycle ergometry include low body oxygen, increased breathing rate, blood pressure changes, increased heart rate, and increased pressure of the fluid around your brain. Based on earlier studies, these risks are very low and outweighed by the benefits of early mobilization. Only FDA approved cycle ergometers will be used in the study. We have set specific rules for stopping the cycling session if you develop a fast heartbeat, low blood pressure, increased breathing, pain, or discomfort during the cycling sessions. The trained research staff applying in-bed cycle ergometry will be at your bedside throughout the session to monitor your vital signs and comfort. You may request to stop cycling at any time and the exercise will end immediately.

Finally, there is a potential risk of a breach of confidentiality and invasion of privacy. To protect against this, we will assign you a unique study identification number. It is this number that will be used to label all study samples and data.

What Are The Benefits of Participating In The Study?

You will receive increased daily oversight by research team members who will be monitoring your condition. The research team will also conduct regular check-ins with your surrogate/family over the course of the trial. Furthermore, you will receive additional testing at discharge to assess physical and mental capabilities. This can help you and your family further understand your current physical and mental capabilities. And finally, you will receive follow up contacts at 3 and 6th months after entering the study to monitor how your recovery is progressing. Follow-up contact and taking an interest in your long-term well-being is above and beyond standard care provided to a patient. All of these benefits are regardless of group assignment and at no cost to you or your family.

In addition, we are trying to learn whether a combination of amino acid supplement and cycle ergometry exercise helps critically ill people with ARF. If you receive these treatments, you may benefit directly from these treatments, but it is unknown at this time whether these treatments are beneficial. This is why we are doing this study.

What Other Options Are There?

Participation in this study is voluntary. The alternative to being in the study is to receive standard clinical care. Amino acid supplementation and cycle ergometry are not routinely given to critically ill patients since the

benefit has not yet been proven, so you are not likely to receive either of these interventions as part of your regular care. Your choice to participate or not in this study will not affect the other medical care you receive.

Are There Any Costs?
There are no costs to you or to your family for your participation in this study. You will not be financially responsible for the cost of treatment directly related to this study, including the costs of the amino acids, additional laboratory tests, ultrasounds or physician examinations. Your health insurance company will not be billed or expected to pay for any costs of participation in this study.

What Is the Compensation?
There is no compensation to you or your family for your participation in this study.

Can You Withdraw or Be Withdrawn From This Study
Should your disease become worse, should side effects become very severe, should new scientific developments occur that indicate the treatment is not in your best interest, or should your physician feel that this treatment is no longer in your best interest, the treatment will be stopped. In addition, the researcher may discontinue your participation in this study at any time.

You may choose to stop participating in this study at any time. You may refuse to participate or may withdraw from the study at any time without penalty or loss of benefits to which you are otherwise entitled. If you are unable to consent for yourself when you are first enrolled in this study, your legally authorized representative (usually a family member or close friend) will make the decision for you. When you are able to consent for yourself, you will be given a separate consent form to sign. On that form you can indicate whether you wish to continue in the study. If you wish to withdraw from the study at that time, you may allow us to keep the samples and data that have been collected up to the time that you withdraw or you can request us to discard the samples and data.

Information Available on ClinicalTrials.gov
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.

What About Confidentiality of Your Health Information?

What health information will be used and disclosed for this study?
The health information we plan to collect for this study is listed below.

- Medical history and examinations
- Information that identifies you, such as your name, address, age, and sex
- Reports from hospital and clinic visits
- Laboratory and other test results
- Ultrasound and CT scan images and reports
- Lists of medications you are taking
- Responses to health surveys and questionnaires

Who is disclosing your health information for this research study?

- The University of Vermont Medical Center
- Other doctors' offices and hospitals where you may receive medical care while this study is active.

Who will use your health information in this study?
Our research team will use your health information. We may also share it with those who assist with the conduct of the research or oversight of the activities for this study. The representatives from the institutions, organizations, and agencies are listed below.

- The University of Vermont and its Committees on Human Research
- The University of Vermont Medical Center
- Research personnel at collaborating sites
- The Clinical Evaluation Research Unit (CERU) at Queen's University in Canada is the Data Coordinating Center for this study. All data entered into the secure electronic data capture system will not contain identifying data of participants.
- The National Institutes of Health (NIH)
- Officials from agencies and organizations that provide accreditation and oversight of research
- Companies that provide drugs or devices for this research project: Baxter International, Inc. and EnableMe
- Your health insurer, for portions of the research and related care that are considered billable
- An independent data and safety monitoring committee
- UVM employees who may reasonably need to access your PHI for the purpose of performing their jobs (e.g., to ensure the integrity of the research, to ensure proper billing for treatment associated with the research, to ensure appropriate grant accounting, for billing and auditing, to maintain records resulting from the research, and for other similar and related matters)

Your health information is protected by a federal law called the Health Information Portability and Accountability Act (HIPAA). Once your health information is shared outside of the University of Vermont Medical Center, we cannot guarantee that these laws will continue to apply. As a result, your health information could be further disclosed for other purposes. In the absence of a Certificate of Confidentiality, it is also possible for a court or other government official to order the release of study data. Refer to the study consent for further information regarding confidentiality. The confidentiality of your health information cannot be guaranteed if you agree it may be used in this study.

How long will your health information be used for research?
Your permission to use your health information will not end until the study is completed. During this study, you will not have access to study data. You may ask for your data once study activities are complete. You have a right to receive a copy of the information in your medical record at any time.

What if you decide not to give permission for research use of your health information?
If you decide not to allow the use and disclosure of your health information, you may not take part in this study. Your decision will have no effect on your current or future medical care.

If you choose to stop taking part in this study in the future, you may cancel permission for the use of your health information. You should let the research team know that you are cancelling your permission. A member of the research team will assist you in making your decision effective. The study will continue to use the health information already collected for the study before you cancelled your permission, and you cannot get back information that was already shared with others.

Who can answer your questions about the use and disclosure of your health information?

If you have questions or concerns about the use and disclosure of your health information, you should ask a member of the study team at 802-847-2193 or the Privacy Officer at The University of Vermont Medical Center, Inc, at (802) 847-2667.

Safeguarding Your Health Information

A record of your progress will be kept in a confidential form at the University of Vermont. The security of your record will be maintained by research personnel working on this study. The results of this study may eventually be published and information may be exchanged between medical investigators, but patient confidentiality will be maintained.

If your record is used or disseminated for government purposes, it will be done under conditions that will protect your privacy to the fullest extent possible consistent with laws relating to public disclosure of information and the law-enforcement responsibilities of the agency.

What Happens If You Are Injured?

If you are injured or become ill as a result of being in this research, The UVM Medical Center, the hospital partner of the University of Vermont, will provide reasonable and usual medical care for that injury or illness. There will be no cost to you if the conditions listed below apply to your injury or illness. These conditions are:

1. The investigator, in consultation with the study sponsor, determines that your injury or illness results from the research and not from your underlying condition or its usual treatment.
2. You let the investigator know about the injury or illness when you first notice it; and
3. You follow medical advice about proper treatment options for the injury or illness.

The UVM Medical Center may claim payments for your medical treatment directly from the study sponsor or your insurance company when these payments are allowed.

For an injury or illness that results from being in this study, the University of Vermont and The UVM Medical Center will not offer you any other payments, such as lost wages or expenses, except for your medical care. Even though you may receive medical care at no cost to you under certain conditions if you are in this study, the UVM Medical Center and the University of Vermont do not admit to any responsibility for an injury or illness that results from being in the study.

If you agree to take part in this study and you sign this consent form, you are not giving up any of your legal rights.

Contact Information

You may contact Dr. Stapleton the Investigator in charge of this study, at (802) 847-1158 for more information about this study. If you have any questions about your rights as a participant in a research project or for more information on how to proceed should you believe that you have been injured as a result of your participation in this study you should contact the Director of the Research Protections Office at the University of Vermont at 802-656-5040.

Statement of Consent

You have been given and have read or have had read to you a summary of this research study. Should you have any further questions about the research, you may contact the person conducting the study at the address and telephone number given below. Your participation is voluntary and you may refuse to participate or withdraw at any time without penalty or prejudice to your present and/or future care.

You agree to participate in this study and you understand that you will receive a signed copy of this form.

_____ _____

Signature of Subject Date

This form is valid only if the Committees on Human Research's current stamp of approval is shown below.

_____

Name of Subject Printed

_____

Signature of Legal Guardian or Legally Authorized Representative Date
(applicable for children and subjects unable to provide consent)

_____

Name of Legal Guardian or Legally Authorized Representative Printed

_____

Signature of Principal Investigator or Designee Date

_____

Name of Principal Investigator or Designee Printed

Name of Principal Investigator: Renee Stapleton, MD, PhD
Address: University of Vermont
Pulmonary & Critical Care Medicine
149 Beaumont Avenue, HSRF 222
Burlington, VT 05405
Telephone Number: (802) 656-7975