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CONSENT FOR RESEARCH
The Pennsylvania State University

Title of Project: **Age Comparisons of Exercising Muscle O2 Supply in Healthy Adults: Effects of Esmolol Infusion**

Principal Investigator: David N. Proctor, PhD

Address: 105 Noll Laboratory
Penn State University
University Park, PA 16802

Telephone Numbers: Weekdays: 8:00 a.m. to 5:00 p.m., (814) 571-5234 or (814) 863-0724

Subject's Printed Name: _____

We are asking you to be in a research study.

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, and there will be no penalty or loss of benefits to which you are entitled.

This form gives you information about the research. Please ask questions about anything that is unclear to you and take your time to make your choice.

KEY INFORMATION

The following is a short summary of this study to help you decide whether or not to be a part of this research. More detailed information is provided later in this form. If you have any questions, be sure to ask the study team.

Why am I being invited to take part in this research study?
We invite you to take part in a research study because we want to understand how the leg muscles use oxygen during exercise.

What is the purpose of this research study?
The purpose of this voluntary research study is to quantify how blood pressure and muscle oxygen delivery are controlled during exercise in young and older women. By using a specific medication that blocks the "fight or flight response" during exercise, we will determine how the human body controls this process.

How long will the research study last?
You will come to the laboratory three times and each visit will take 3 to 4.5 hours.

What will I need to do?
For this study, you will be asked to perform bicycle exercise and handgrip exercise on several occasions while we measure your breathing, blood pressure, heart rate, and leg muscle oxygen level. During one session, you will receive an infusion of esmolol (a heart rate lowering medication) into an arm vein.

What are the main risks of taking part in the study?

For this study, the main risks to know about are: fatigue and leg muscle discomfort due to the bicycle exercise, forearm soreness from the handgrip exercise, and soreness and bruising from the infusion of esmolol (a heart rate lowering medication) into an arm vein.

What are the possible benefits to me that may reasonably be expected from being in the research?
There are no benefits to you from taking part in this research. Results of the study may benefit other people in the future by helping us learn more about how to body controls blood pressure and leg blood flow during exercise.

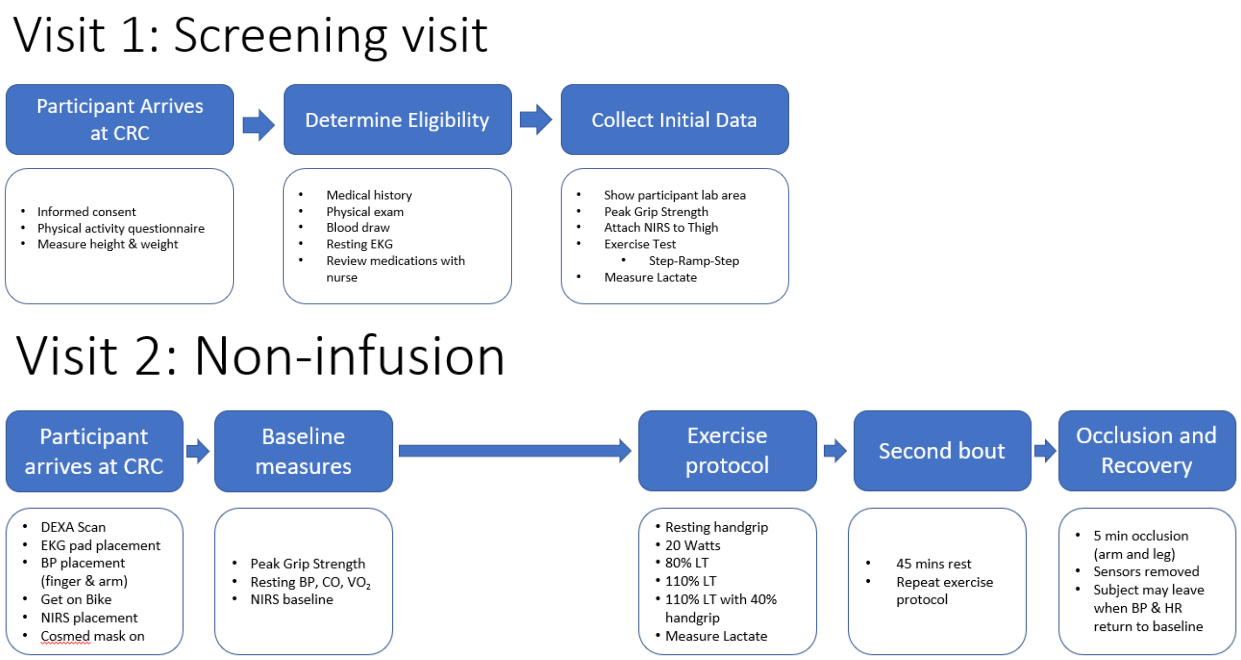
What happens if I do not want to be in this research?
Participation in research is completely voluntary. You can decide to participate or not to participate.

DETAILED INFORMATION
The following is more detailed information about this study in addition to the information listed above.

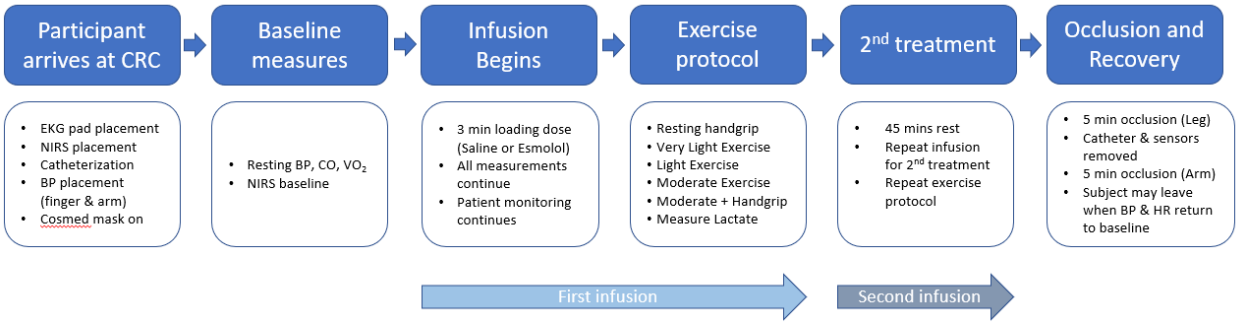
1. **Why is this research study being done?**
   This research is being done to find out how age affects oxygen delivery during exercise in women when the amount of blood their heart can pump is reduced. To do this, we will infuse an FDA approved drug called esmolol (through an arm vein) which temporarily blocks beta-1 receptors (receptors in the heart which are involved in the "fight or flight response") during recumbent cycling exercise.

   Approximately 28 people will take part in this research study in the State College area.

2. **What will happen in this research study?**



Visit 3: Infusion



Visit 1 (screening visit)

You will be asked to avoid alcohol, over the counter cold prep and NSAIDs, and strenuous exercise for 24 hours, and to eat a small meal 2-3 hours prior to coming to the laboratory. You will also be asked to refrain from items containing caffeine 12 hours prior to this visit. For your safety, you must tell the study doctor or nurse about all the prescription drugs, herbal products, over-the-counter drugs (OTC), vitamins and other supplements you are taking. Check with the study doctor before starting any new medicines (including prescription, OTC drugs, vitamins and herbal supplements) or changing doses of medications that you are already taking.

Women who are currently taking hormone therapy of any kind (oral contraceptives, estrogen replacement, etc) will not be excluded from participation in this study. However, we will ask 1) pre-menopausal women to indicate their current menstrual status and oral contraceptive use and 2) post-menopausal women to self-report their history and duration of sex hormone replacement. This information will be collected at the time of your medical history/physical exam.

During this first visit, you will be given sufficient time to read this consent form and ask questions. If you are a woman of childbearing potential (pre-menopausal), you will take a urine pregnancy test to ensure you are not pregnant. Your participation in this research will end if you test positive. Medical personnel will then perform a brief physical examination and you will then complete a medical history questionnaire and a physical activity history questionnaire. While filling out these questionnaires, you are free to skip any questions you would prefer not to answer. A venous blood draw will then be performed (7.5 mL total) by a CRC nurse and sent for analysis to ensure your blood cell counts and kidney and liver function are within normal limits before continuing the study. This will be followed by measurements of your height, weight, waist circumference, blood pressure and a resting EKG (tracing of your heart electrical activity). During this first study visit, you will also be asked to squeeze a handgrip device as hard as you can 3 times, with approximately 1 minute of rest between each. After a short recovery, you will then be asked to squeeze the handgrip device for approximately 90 seconds at 40% of your maximum effort. Immediately after, we will ask you how difficult you found the 40% grip task using a rating of perceived effort scale.

You will then lay on an exam bed for placement of EKG pads and a doppler ultrasound device will be used to determine skinfold thickness of your thigh. NIRS sensors will then be placed (one on the forearm, one on the forehead, and two on the leg). You will then be assisted onto the recumbent bike. A silicone face mask will be placed over your nose and mouth to monitor your oxygen consumption and breathing frequency, and blood pressure devices will be placed over your arm (SunTech Tango) and finger

(Finometer). After all instrumentation is in place, baseline measurements of heart rate, cardiac output, oxygen consumption, blood pressure, and NIRS will begin.

You will then be asked to complete three exercise bouts on a recumbent (feet behind the pedals) bike. The first bout will consist of very light pedaling for 2 minutes (warm-up) followed by approximately 6 minutes of pedaling at what should be a moderate effort for you. After a few minutes of rest and/or light pedaling (recovery), you will be asked to perform a second bout of exercise, which will consist of a very gradual increase in workload ("ramp") until you can no longer maintain the required pedal speed or need to stop due to fatigue. This second bout will likely last between 6 and 12 minutes. After a few minutes of light pedaling, we will remove your face mask and let you recover in a comfortable chair. After 30 minutes of recovery, we will assist you back on the bike and will reattach your facemask. We will then have you pedal for 2 minutes at a very light workload, followed immediately by up to 12 minutes of pedaling at moderately heavy workload. After a brief cool-down of light pedaling, we will remove the facemask and other sensors (e.g., EKG, NIRS, etc). At several points throughout this visit (minimum of 3, maximum of 6) we will collect a small drop of blood from your fingertip to measure the level of lactate in your blood. The measurements obtained during this first study visit will determine the exercise workloads that will individually selected for you during study visits 2 and 3.

Analysis of the blood tests, EKG and medical history/exam results, and your tolerance to the handgrip and cycling exercise will collectively determine if you are eligible to continue the study. Eligible participants will be asked to return to the CRC for two experimental visits (non-infusion visit and infusion visit) at least 48 hours apart. Visit 1 will take up to 3 hours to complete.

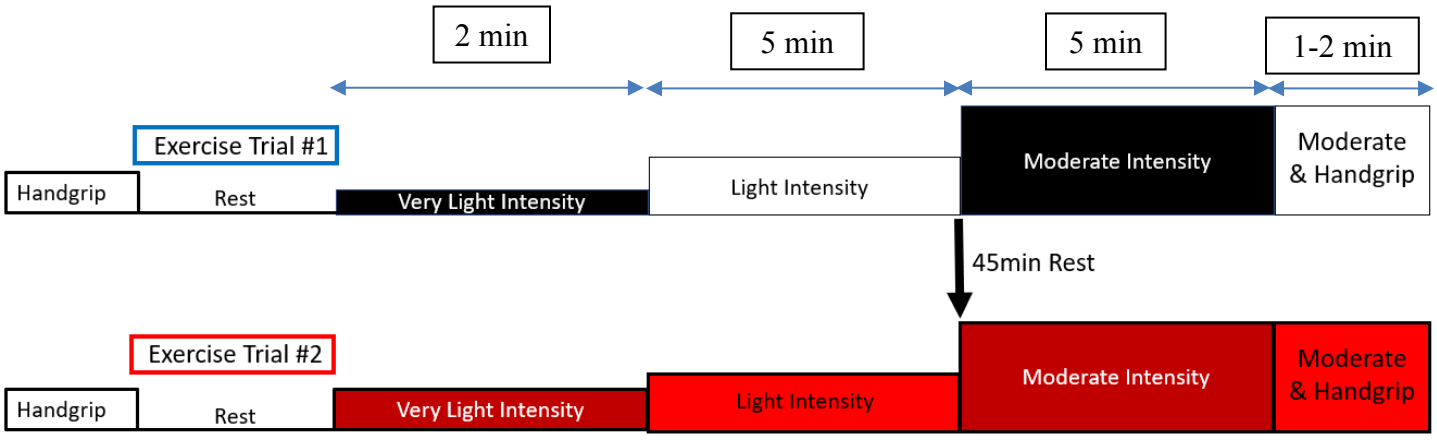
Visit 2 (non-infusion)

As with the screening visit, you will be told to avoid alcohol, over the counter cold prep and NSAIDs, and strenuous exercise for 24 hours, and to eat a small meal 2-3 hours prior to coming to the laboratory. Women of childbearing potential (pre-menopausal) will take a urine pregnancy test to ensure they are not pregnant.

You will then be asked to lay still while you are scanned with a Dual-energy X-ray absorptiometry (DEXA) device to determine your body composition (fat, muscle, bone).

Then you will lay on an exam bed for placement of EKG pads and near-infrared sensors (NIRS) will be taped over a forearm muscle, your forehead, and two leg muscles (thigh and calf).

We will then assist you onto the recumbent bike. After repeating your peak grip strength test from visit 1, a silicone face mask will be placed over your nose and mouth to monitor your breathing. A blood pressure cuff will be placed over your arm and a small blood pressure device will be placed on a finger. After all instrumentation is in place, baseline measurements will begin.



All measurements will continue to be collected throughout the exercise trials. Once these measurements have stabilized, you will be asked to squeeze the handgrip device at 40% of the maximum force during the maximum grip testing for 1 to 2 minutes. Once all measurements have returned to baseline, you will then begin the cycling exercise protocol (see figure above). You will be asked to pedal for 2 minutes at a very light intensity, followed immediately by 5 minutes of cycling at a light intensity, and 5 minutes of cycling at a moderate intensity. Finally, the you will continue cycling at the same intensity for 1 to 2 minutes while simultaneously squeezing a handgrip device at 40% of your maximal effort. You will then rest for 45 mins, after which you will repeat the exercise protocol. Immediately following the second exercise bout, cuffs will be placed on the upper arm and on the upper thigh of the limbs with the NIRS probes attached. The cuffs will then be inflated to ~250 mmHg until the limbs have been completely deoxygenated (approximately ~5 minutes).

At least three lactate measurements will be collected during each trial (6 total); one during rest, one after 4 mins of light intensity exercise, and one after 4 mins of moderate intensity exercise.

After the recovery period, most instrumentation will be removed (except for the blood pressure cuffs and EKG). You will then be asked to sit up slowly and will be offered juice and crackers. Once your blood pressure and heart rate have returned to normal, we will remove the remaining monitoring equipment and you may leave. Visit 2 will take up to 3.5 hours to complete.

Visit 3 (Infusion)

As with the previous visits, you will be told to avoid alcohol, over the counter cold prep and NSAIDs, and strenuous exercise for 24 hours, and to eat a small meal 2-3 hours prior to coming to the laboratory. You will also be asked to refrain from items containing caffeine 12 hours prior to this visit.

Women of childbearing potential (pre-menopausal) will take a urine pregnancy test to ensure they are not pregnant. Then you will lay on an exam bed for initial instrumentation (placement of EKG pads and blood pressure cuffs) and measurement of vital signs. A nurse will then insert a catheter into one of your arm veins. This catheter will be used to infuse the drug (Esmolol or saline) and to withdraw a blood sample at the beginning and end of the study.

Final instrumentation will include 1) placing a silicone face mask over your nose and mouth to monitor your oxygen consumption and breathing frequency, and 2) taping a near-infrared sensors (NIRS) over your forearm muscle, on your forehead, over a thigh muscle and over one of your calf muscles.

After all instrumentation is in place, you will be seated on the recumbent ergometer and baseline measurements of heart rate, cardiac output, oxygen consumption, blood pressure, and NIRS will begin.

A CRC clinician will join the research team immediately before it is time to start the infusion. The CRC clinician will be able to review the EKG results at that time if there are any concerns. You will then be randomly assigned to one of two treatment orders. You will either receive an infusion of esmolol during the first exercise trial and saline during the second trial or you will receive and infusion of saline during the first trial and esmolol during the second trial. Neither you nor the research team will know which treatment order you have been assigned until after all participants have completed the study. Only the clinician operating the infusion pump will know your treatment order. Esmolol dose will be based on your fat free mass (determined by DEXA).

All measurements will continue to be collected throughout the exercise protocol. Once these measurements have stabilized (approximately 10 minutes into the infusion), you will be asked to squeeze the handgrip device at 40% of your maximum force for 1 to 2 minutes. Once all measurements have returned to baseline, you will then begin the cycling exercise protocol. You will be asked to pedal for 2 minutes at a very light intensity, followed immediately by 5 minutes of cycling at a light intensity, and 5 minutes of cycling at a moderate intensity. Finally, you will continue cycling at the same intensity for 1 to 2 minutes while simultaneously squeezing a handgrip device at 40% of your maximal effort. Once the infusion stops, the IV line will be flushed. You will then rest for 45 mins, after which you will repeat the exercise protocol while receiving the second infusion (esmolol or saline). Immediately following the second exercise bout, a cuff will be placed on your upper arm and upper thigh of the limbs with the NIRS probes attached. The cuffs will then be inflated to ~250 mmHg until your limbs have been completely deoxygenated (approximately 5 minutes).

After the recovery period, most instrumentation will be removed (except for the blood pressure cuffs and EKG). You will then sit up slowly and will be offered juice and crackers. Once your blood pressure and heart rate have returned to normal, we will remove the remaining monitoring equipment and you may leave. Visit 3 will take up to 4.5 hours to complete.

What are your responsibilities if you take part in this research?

For your safety, you must tell the study doctor or nurse about all the prescription drugs, herbal products, over-the-counter drugs (OTC), vitamins and other supplements you are taking. Check with the study doctor before starting any new medicines (including prescription, OTC drugs, vitamins and herbal supplements) or changing doses of medications that you are already taking.

3. What are the risks and possible discomforts from being in this research study?

- **Confidentiality**: There is a risk of loss of confidentiality if your information or your identity is obtained by someone other than the investigators, but precautions will be taken to prevent this from happening. The confidentiality of your electronic data created by you or by the researchers will be maintained to the degree permitted by the technology used. Absolute confidentiality cannot be guaranteed.

- **Pregnancy**: It is important that a fetus not be exposed to any unnecessary risks; therefore, pregnant women will not be studied. A urine pregnancy test will be administered at the beginning of all experimental visits to all women of childbearing potential to ensure they are not pregnant.

- **Blood pressure, heart rate:** Minimal risk of skin irritation from EKG patches.

- **Oxygen Consumption:** No risk

- **IV placement:** The discomfort associated with a blood draw/IV placement is a slight pinch or pinprick when the sterile needle enters the skin. The risks of a blood draw include mild discomfort and/or a black and blue mark at the puncture site. Less common risks include infection or bleeding at the puncture site, or on rare occasions, dizziness, light-headedness, nausea or fainting during the procedure. To minimize the risk of infection, aseptic techniques will be used.

- **Esmolol infusion:** The risks stated by the manufacturer include heart block, hypotension, injection site pain, nausea, seizure, bronchospasm, allergic reaction, infusion site reaction, or extravasation (leaking of infusion into tissue around the IV site which may cause tissue death). However, in our experience these symptoms have never occurred in our research participants. The infusion will end if HR falls by more than 20 beats/min or below 40 beats/min or symptoms occur, or if symptomatic hypotension occurs (mean blood pressure drop of more than 20mmHg and/or symptoms). If extravasation would occur, we would proceed as follows:
    - Stop infusion
    - Apply warm compress over the catheter site
    - Elevate the arm
    - Observe/monitor for at least 45 minutes (i.e. 5 half-lives for Esmolol)
    - Call subject within 24 hours

- **Saline infusion:** no risk

- **Skinfold of the forearm and leg to measure fat thickness**: No risk

- **Recumbent cycling exercise:** Cycling exercise will cause fatigue, shortness of breath, elevated body temperature and muscle fatigue. Could also cause chest discomfort and/or dehydration. These effects typically disappear shortly after exercise.

- **Isometric handgrip exercise**: Handgrip exercise will cause fatigue in the forearm. This may be associated with a burning sensation in the forearm and possible muscle soreness after the test.

- **Post exercise occlusion:** The upper arm and upper leg cuff occlusions may result in a tingling or burning sensation in the limbs. This will subside once the cuffs are released.

- **NIRS**: No risk

- **DEXA**: There is a very small chance of cancer from exposure to radiation. However, given the small amount of radiation used, this is very unlikely.

- **Finger blood lactate measurement:** A slight pinch or pinprick when the sterile needle enters the skin. The risks include mild discomfort and/or a black and blue mark at the puncture site. Less common risks include infection or bleeding at the puncture site, or on rare occasions, dizziness, light-headedness, nausea or fainting during the procedure. To minimize the risk of infection, aseptic techniques will be used.

- **PhysioFlow:** Preparation for the PhysioFlow device requires rubbing the skin where patches will be applied with an abrasive gel (Nuprep) that will cause some skin irritation and may cause mild inflammation.

- **Order of measurements:** There are no additional risks to omitting or changing the order of the hemodynamic measurements in this study.

- **Risk of incidental finding:** There is a rare risk of an incidental finding. The testing performed during this study is intended solely for research purposes and will not be utilized to detect any medical condition. However, if we notice something unusual, we will consult one of the cardiologists on the research team to determine if it merits follow-up. If so, we will contact you within 48 hours and suggest that you follow up with your private medical provider. To facilitate follow-up care, a copy of the data may be provided upon request. You will be monitored continuously for adverse effects and the medical personnel will remain in the room during the study.

- There may be risks that are currently unknown.

4. What are the possible benefits from being in this research study?

4a. What are the possible benefits to me?

You will not directly benefit from this study.

4b. What are the possible benefits to others?

Scientists may better understand how aging in women affects oxygen delivery when the heart's ability to pump blood is reduced.

5. What other options are available instead of being in this research study?

You may choose not to be in this research study.

6. How long will I take part in this research study?

Overall, your participation in this research study should involve 3 study visits. Visit one will last up to 3 hours. Visit two will last up to 3.5 hours. Visit 3 will last up to 4.5 hours. We anticipate that all study visits will be completed within one month.

7. How will you protect my privacy and confidentiality if I decide to take part in this research study?

7a. What happens to the information collected for the research?

Efforts will be made to limit the use and sharing of your personal research information to people who have a need to review this information. Reasonable efforts will be made to keep the personal information in your research record private. However, absolute confidentiality cannot be guaranteed.

- A list that matches your name with your code number will be kept by the research nurses on a protected network program called RedCap.
- Your research records will be kept on a password-protected computer in the Cardiology research lab and only labeled with your study ID code. The paper copy of your chart will be kept in locked file cabinets in locked rooms in the Clinical Research Center (CRC).

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. This means that the researchers cannot disclose information that identifies you to anyone not connected with the research. This protection also prevents this information from being used or disclosed for legal proceedings, such as being accessed through a court order. The Certificate of Confidentiality however does not prevent disclosures required by law, such as information about child abuse or neglect and harm to yourself or others. Also, your information may be disclosed in accordance with any consent you provide, including for your medical treatment or use in other research. Additionally, the Certificate of Confidentiality does not prevent your information from being disclosed to the National Institutes of Health in order for it to evaluate or audit the research, or prevent disclosures required to meet FDA requirements. For additional information ask the principal investigator or a member of the study team or contact the Human Research Protection Program at (814) 865-1775.

In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.

We will do our best to keep your participation in this research study confidential to the extent permitted by law. However, it is possible that other people may find out about your participation in this research study. For example, the following people/groups may check and copy records about this research.

- The Office for Human Research Protections in the U. S. Department of Health and Human Services
- The research study sponsor, the National Institutes of Health.
- The Institutional Review Board (a committee that reviews and approves research studies) and Penn State's Human Research Protection Program.

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.

U.S. Food and Drug Administration may check and copy records about this research.

7b. What will happen to my research information and/or samples after the study is completed?
Your information or samples that are collected as part of this research will not be used or distributed for future research studies, even if all of your identifiers are removed.

Most tests done on samples in research studies are only for research and have no clear meaning for health care. If the research with your identifiable information or samples gives results that do have meaning for your health, the researchers will contact you to let you know what they have found.

8. What are the costs of taking part in this research study?

8a. What will I have to pay for if I take part in this research study?
You will not be charged for any test or procedure performed as part of this research study.

8b. What happens if I am injured as a result of taking part in this research study?
In the unlikely event you become injured as a result of your participation in this study, medical care is available. It is the policy of this institution to provide neither financial compensation nor

free medical treatment for research-related injury. By signing this document, you are not waiving any rights that you have against The Pennsylvania State University for injury resulting from negligence of the University or its investigators.

9. Will I be paid to take part in this research study?

You will receive a total of $150 for completing this study.

- You will not be paid for completing visit 1.
- You will be paid $50 for completing visit 2.
- You will be paid $100 for completing visit 3.

If you do not complete the study for any reason, you will be paid for the visits you have completed. You will need to provide your social security number and address to receive a check for payment and for tax reporting purposes.

10. Who is paying for this research study?

The investigators are receiving a grant from The National Institutes of Health (NIH) to support this research.

11. What are my rights if I take part in this research study?

Taking part in this research study is voluntary.

- You do not have to be in this research.
- If you choose to be in this research, you have the right to stop at any time.
- If you decide not to be in this research or if you decide to stop at a later date, there will be no penalty or loss of benefits to which you are entitled.

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 medical information from your routine medical care. If you agree, this data will be handled the same as research data. If you withdraw completely from the research study, no further information will be collected and your participation will end. You may discontinue taking part at any time without penalty or loss of benefits to which you are otherwise entitled.

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 not being able to place an intravenous catheter or not being able to perform the exercises in this study.

During the course of this research, you will be provided with any new information that may affect your health, welfare or your decision to continue participating in this research.

12. If I have questions or concerns about this research study, whom should I call?

Please call the head of the research study (principal investigator), Dr. Proctor at 814-863-0724 (office) or 814 571-5234 (cell) or the staff at the CRC 814-865-5811 if you:

- Have questions, complaints or concerns about the research.
- Believe you may have been harmed by being in the research study.

You may also contact the Human Research Protection Program at (814) 865-1775, IRB-ORP@psu.edu if you:

- Have questions regarding your rights as a person in a research study.
- Have concerns, complaints, or general questions about the research.

- You may also call this number if you cannot reach the research team or wish to offer input or to talk to someone else about any concerns related to the research.

You may visit the Human Research Protection Program website at https://www.research.psu.edu/irb/participants for:

- Information about your rights when you are in a research study;
- Information about the Institutional Review Board (IRB), a group of people who review the research to protect your rights; and
- Links to the federal regulations and information about the protection of people who are in research studies. If you do not have access to the internet, copies of these federal regulations are available by calling the HRPP at (814) 865-1775.

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

INFORMED CONSENT AND AUTHORIZATION TO TAKE PART IN RESEARCH
Signature of Person Obtaining Informed Consent

Your signature below means that you have explained the research to the subject or subject representative, provided the subject or subject representative an opportunity to discuss and consider whether or not to participate in the research, and have answered any questions about the research.

_____	_____	_____	_____
Signature of person who explained this research	Date	Time	Printed Name

(Only approved investigators for this research may explain the research and obtain informed consent.)

Signature of Person Giving Informed Consent and Authorization
Before making the decision about being in this research you should have:

- Discussed this research study with an investigator,
- Read the information in this form, and
- Had the opportunity to ask any questions you may have.

Your signature below means that you have received this information, have asked the questions you currently have about the research and those questions have been answered. You will receive a copy of the signed and dated form to keep for future reference.

Signature of Subject

By signing this consent form, you indicate that you voluntarily choose to be in this research and authorize your information to be used and shared as described above.

_____	_____	_____	_____
Signature of Subject	Date	Time	Printed Name