Participant Name:_____ **Date:** _____

Title of Study: Immune Function and Muscle Adaptation to Resistance Exercise in Older Adults

Principal Investigator: Richard Dennis, PhD

VAMC: Central Arkansas Veterans Healthcare System, 598 Version 5, Date 04-26-16

NCT02261961

INTRODUCTION

You are being invited to take part in a research study that is being carried out at the Central Arkansas Veterans Health Care System. Before you decide to take part, it is important for you to know why the research is being done and what it will involve. This includes any potential risks to you, as well as any potential benefits you might receive. The sponsor of the study is the VA Rehabilitation Research and Development service.

Read the information below closely, and discuss it with family and friends if you wish. Ask one of the study staff if there is anything that is not clear or if you would like more details. Take your time to decide. If you do decide to take part in this study, your signature on this consent form will show that you received all of the information below, and that you were able to discuss any questions and concerns you had with a member of the study team.

BACKGROUND AND PURPOSE

- This research seeks to better understand the cellular and molecular biology that controls the loss of skeletal muscle during aging and the gain in skeletal muscle in response to weight lifting or strength training. Specifically, we are investigating the influence of the immune system and nutritional supplementation on muscle health. The research does not involve genetic testing.
- The study is being conducted by the scientists and physicians of the Geriatric Research Education and Clinical Center of the Central Arkansas Veterans Healthcare System.
- You have been asked to participate because you are a veteran, age 60-80 years, and are interested in participation in a study that involves strength training and nutritional supplementation.
- Muscle strength strongly affects personal capabilities and independence in older adults. However, the ability to maintain muscle during aging or gain muscle through exercise varies considerably. Thus, the knowledge gained from the study will hopefully be used to improve muscle maintenance and rehabilitation strategies through exercise and nutritional supplementation.
- The nutritional supplement and placebo being used in the study are available commercially as food products but have not been tested or approved by the Food and Drug Administration for the treatment, cure, or prevention of any disease.
- The study expects to enroll 50 participants.

DURATION OF THE RESEARCH

- The expected duration of the study is four years.
- Each individual's participation in the study will last approximately one year. The collection of information from your VA medical record will conclude with a final review for safety purposes approximately 30 days after your last research visit.
- Participants must attend approximately 50-60 visits at the North Little Rock VA medical center. Some flexibility will be allowed in scheduling but please contact study staff immediately anytime a scheduling conflict arises.

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- The majority of visits will last approximately an hour though a few will be longer or shorter. Two appointments are unusually long and require approximately four hours.
- The procedures that occur at these visits are described below.

STUDY PROCEDURES

If you decide to take part in this study, the certain procedures will be required. The procedures are being performed by the study team or you for research purposes only and are not part of your standard medical care. You cannot take part in this study if you are currently enrolled in another interventional study. The purpose, risks, and benefits of each procedure will be explained to you by the study team and you should ask questions as they come to mind.

- **Medical Exam:** A medical history and physical exam will be conducted by the study physician in order to determine if you are healthy enough to safely participate. The exam will include exercise and an electrocardiogram to evaluate your heart health. The exam may be repeated during the study if additional information is needed to ensure that you can continue safe participation. Information will be collected from you, your medical record, and if needed, from your healthcare providers inside or outside the VA.
- **Nutritional Supplementation:** Half of the participants will drink the nutritional supplement and half will drink a placebo (sugar flavored beverage). The drink must be consumed twice daily for approximately ten months. The supplement and placebo are both orange-flavored powder that is mixed in water for consumption. The drinks are only to be consumed by you and cannot be shared with others. During participation you must maintain your normal diet and you cannot begin taking any new nutritional supplements outside of the study. Also during participation, you cannot consume any protein or amino acid supplements such as whey protein or Ensure.
- **Randomization:** Your drink assignment will be random, like flipping a coin, which gives you an equal chance of being in the supplement or placebo group. It is important that the study staff and other participants not know which group you are in. Thus, please do not discuss what your drink looks like or tastes like with these individuals. If you have questions, there is a study monitor who you can talk to.
- **Compliance:** You must document your consumption of the drink twice daily on a provided calendar. We ask that you complete the calendar honestly as it is understandable that you may forget or be unable to have two drinks on some days. Do not dispose of any unused portion of drink or the containers. There will be approximately 10 visits where you must return the used drink containers (even if they are empty) and pickup new containers. At these visits you will meet with the study monitor to review your compliance with the drinking requirements and any issues you may be having. It is very important that you bring your drink calendar and the used canisters to these visits. It is a requirement to receive your study compensation for these visits. However, if you forget your calendar or canisters, you will receive that payment when you bring them to your next visit.
- **Exercise Training:** You will participate in a strenuous exercise training program for the thigh muscles at the North Little Rock VA three times per week (Mon, Wed, and Fri) for approximately three months. There will be approximately 40 visits involving supervised exercise and each will last about an hour. You are not allowed to perform weight lifting exercises with your legs outside of the study though other forms of exercise such as walking or upper body weight lifting are acceptable.

Participant Name:_____ **Date:** _____
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- **Functional Assessments:** Your strength will be measured regularly during the study and approximately every two weeks during the exercise training. Your balance and gait (walking speed) will be evaluated four times during the study.
- **Muscle Size:** The size and composition (percent bone, fat, and muscle) of your thighs will be measured by CT (computed tomography) scan. The procedure will be performed by the Imaging Service at the Little Rock VA. The procedure will occur three times: at study beginning, after completion of the training program, and at the end of your participation. The scan will require that you lay still in the scanner for approximately 15 minutes.
- **Post-Training Follow-Up:** After completion of the exercise training program, your muscle strength and function will continue to be monitored for approximately six months of post-training follow-up. There will be approximately 10 more visits during this time. During this six months, you will not be allowed to perform weight lifting exercises with your legs outside of the study though other forms of exercise such as walking or upper body weight lifting are acceptable.
- **Vaccination:** Participation requires that you receive a triple-vaccine against tetanus, diphtheria, and pertussis diseases from the study physician or unit nurse. The vaccine is also known as TDAP. The study is using the vaccine to determine how well your immune system responds. You will not be allowed to participate if you have had this vaccination in the past two years.
- **Blood Draws:** Blood will be drawn nine times during the study most likely from your arm vein by a phlebotomist or nurse. The total amount each time will be less than two ounces or 60ml. The blood will be used as part of your eligibility screening, for monitoring the safety of participation, and for research laboratory tests. The majority of the blood draws will occur in the first two months of participation. An extra blood draw could be needed for unforeseen circumstances such as the physician needs to follow-up on an abnormal laboratory result.
- **Muscle Biopsies:** The study physician will collect muscle tissue by biopsy five times during the study. Four biopsies will occur during the first few weeks of the study and the last biopsy will be several months later after completion of the exercise training program. The physician will numb a small area of your thigh. A small incision will be made so that a needle can be used to collect 2-3 pieces of muscle about the size of a pea. If the amount of muscle needed is not obtained, up to 2 more needle insertions may be made with your permission. The time required for needle insertion and withdrawal is less than 30 seconds. An IV catheter may be inserted into your arm vein prior to the procedure as a precautionary step should an emergency occur that requires immediate drug administration. The muscle will be used for research laboratory tests related to your molecular and cellular response to the nutritional supplement and the exercise.
- **Staff Contact:** The study staff will contact you regularly, using the contact information provided or present in your medical record, during and possibly up to approximately 30 days after completion of your participation for issues related to issues such as scheduling, reminders to consume your drink, and to confirm your wellness. These issues may require that you attend additional visits. If you withdraw from the study and wish to have no additional contact with the study staff, you may inform the study staff and they will respect your wishes.
- **Voluntary Participation:** Participation in all of the above procedures is completely voluntary. You are not required to participate in any procedure or answer questions that you chose not to. However, this refusal may prevent your further participation in the study.

Participant Name:_____ **Date:** _____
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POSSIBLE RISKS OR DISCOMFORTS

Any procedure has possible risks and discomforts. The procedures in this study may cause all, some, or none of the risks or side effects listed. Rare, unknown, or unexpected risks also may occur. The common risks of this study are not serious; though there are serious risks that are less common or rare. Participation may exacerbate pre-existing health conditions.

The study tries to exclude individuals at greater than normal risk from the study procedures. However, please report any unusual symptoms or problems to the study staff. Their 24-hour contact number is listed near the end of this form.

If in the opinion of the principal investigator your participation is no longer appropriate for the study, your participation may be discontinued against your wishes. This would apply if you do not comply with the requirements for participation or if it becomes medically unsafe for you to continue.

- **Nutritional Supplementation**
  - Nutritional Supplement: Taking the nutritional supplement is considered low risk. However, the following conditions could be made worse: allergies or asthma, herpes, and low blood pressure. Mild side effects are possible including abdominal pain, bloating, diarrhea, gout, blood abnormalities, and sensitivity similar to monosodium glutamate (MSG; headache, flushing, tingling, weakness). Caution should be used when taking the supplement and lactulose. The supplement should not be taken by individuals undergoing chemotherapy, or those having a recent heart attack, liver disease, seizures, mania or bipolar disorder and taking lithium.
  - Placebo: The placebo contains 16 grams (60 calories) of sugar. The study physician does not feel that this amount of sugar taken twice daily is a risk for diabetic participants. However, if you are diabetic you should be aware that your blood sugar measurements may be elevated if taken shortly after the drink. You may ask questions when our physician discusses this issue with you.
- **Exercise Training**
  - You will have to work hard during the exercise training program. The weight-lifting will be strenuous and will likely cause temporary soreness in the thigh muscles or joints of your legs, but these discomforts should not result in disability or incapacity.
  - Exercise may cause (estimated at 1 of 100 cases or 1:100) shortness of breath, chest pain, or dizziness; and ligament, tendon, or muscle sprain.
  - Heart problems are a rare but serious risk of strenuous exercise and may result in sudden death (1:18,000 adults per year).
  - If you feel unwell at any time during exercise, immediately notify the exercise supervisor so that the exercise can be halted and you can be evaluated and appropriate action can be taken.
- **CT Scan:** The procedure exposes subjects to radiation. The total amount of radiation per scan (6 mSv) is approximately the same as the average exposure an individual has from natural sources per year. Having three scans in one year creates a very small increase (from 44.9% to 44.95%) in the risk of cancer for the average 70 year old male (www.xrayrisk.com).
- **Vaccination:** The most common problems in adults are mild or moderate in severity. Common problems include pain or redness and swelling at the injection site. Fever, headache, tiredness, or upset stomach may also occur. Chills, body aches, rash, or swollen glands are possible but

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Title of Study: Immune Function and Muscle Adaptation to Resistance Exercise in Older Adults
Principal Investigator: Richard Dennis, PhD
VAMC: Central Arkansas Veterans Healthcare System, 598 Version 5, Date 04-26-16

uncommon. A severe allergic reaction could occur after any vaccine but is rare. Individuals who have had an allergic reaction or other serious unexplained problems after vaccination, or has had Guillian-Barre Syndrome should not be vaccinated.

- **Blood Draws:** You may feel a small amount of pain or feel and possibly feel lightheaded or faint. The blood draw will likely cause a bruise. There is also a small risk of infection. These risks also apply should an IV catheter be used during your muscle biopsies.
- **Muscle Biopsy**
  - Prior to the muscle biopsies you must refrain from taking products that can influence bleeding. Aspirin products and certain supplements must not be used for 10 days prior to the procedure. Non-aspirin non-steroidal anti-inflammatory drugs such as ibuprofen must not be taken for 3 days prior to the procedure. You will be reminded and given a list of the products from which to refrain.
  - The procedure may cause discomfort. Injection of the local anesthetic may sting. The discomfort of the biopsy needle insertion varies from painless to uncomfortable or painful. The site will be bruised and sore for a few days and will likely cause a small scar.
  - Temporary numbness of the skin at the biopsy site can occur. Infection of the wound is rare. Other risks include an allergic reaction to the local anesthetic, feeling light-headed or fainting during the procedure, or that the wound resumes bleeding later in the day (1:100 cases each).
  - The biopsy site will be bruised and sore for a few days. The biopsy should not interfere with your normal daily activities other than the wound must be kept dry for 3 days with the exception of showering (i.e. no bath or hot-tub).
  - You will be contacted by the study staff later in the day after your biopsy to confirm wellness. However, at any time the site is more painful than just sore, you should contact the study staff at the 24-hour number listed in this form.
- **Standard Medical Care:** Risks of the usual care you receive are not risks of the research. Those risks are not included in this consent form. You should talk with your health care providers if you have any questions about the risks of usual care. Participation in research may involve a loss of privacy. Your research records will be kept as confidential as possible.

CONFIDENTIALITY

- The study will collect research data and personal information about you. This is required for participation but could result in a loss of privacy. However, your research data will be treated the same as any VA medical record and kept as confidential as possible.
- Your data and specimens will be labeled by a code that does not contain any information that can be used to identify you such as social security number, initials, or birth date. The master list linking names to code numbers will be kept separately from the research data. Only authorized individuals will have access to this master list and any other research documents or specimens. Research documents and specimens are stored according to VA security standards such as in locked files or freezers and if electronic then using limited access folders on the VA server. Research records are currently maintained until six years after study closure.
- Your identity will not be revealed in any reports or publications resulting from this study.

Participant Name:_____ **Date:** _____
Title of Study: Immune Function and Muscle Adaptation to Resistance Exercise in Older Adults
Principal Investigator: Richard Dennis, PhD
VAMC: Central Arkansas Veterans Healthcare System, 598 Version 5, Date 04-26-16

- The study team includes investigators from the University of Arkansas for Medical Sciences. The study may also involve other non-VA institutions such as another university or service provider. These institutions may be involved in the analysis of your coded data or specimens. However, they will never have access to any of your personal identifiers.
- In addition to the study team, other persons authorized to access research information may include regulatory agencies such as the Food and Drug Administration (FDA), the Government Accounting Agency (GAO) or the Office for Human Research Protection (OHRP), Office of Research Oversight (ORO), as well as members of the VA Research Administration. By signing this document, you consent to their inspections of the research information.
- The Department of Veterans Affairs (VA) requires some information to be recorded in the VA electronic medical record for all research participants. If you are a Veteran who is a patient at the VA Medical Center, a copy of your signed and dated consent and HIPAA forms will be placed in your medical record.
- If you are a Veteran but do not have an electronic medical record at this VA Medical Center, you will need to provide a copy of your DD214 to the eligibility office so that a record may be created for you before you provide informed consent to participate.
- 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.
- This form does not give the study physician permission to access, record, and use your private health information. You will be given a separate HIPAA form which provides more information about how your private health information will be used in this study, who will have access to your records, and how you can revoke (take back) your permission in the future. You will not be able to participate if you do not sign the HIPAA authorization form.

POTENTIAL BENEFITS

Individuals may or may not benefit from participation in this research study, but the information cannot be obtained by alternative procedures. The study team feels that important scientific knowledge will be gained and that this information may benefit society in the future. When participating in research, you should feel that the overall benefit of participation is greater than the risk.

- Participants may or may not benefit from the nutritional supplement. The study is testing whether the supplement improves the responses to vaccination and to exercise training and the maintenance of muscle strength post-training. If you desire to know what product you were taking after completion of the study, you may call the VA Research Pharmacist at 501-257-6382.
- The muscle biopsy, blood draws, and CT scan will not benefit the participants. The procedures will possibly provide data that increases our understanding of the relationship between immune function and muscle health and can be used to improve strategies for muscle maintenance during aging and muscle rehabilitation when needed.
- If you request a copy of the clinical laboratory results for your blood, they will be provided to you and you may discuss them with our physician. However, you will not be informed of any of your specific research laboratory results as this information has no proven medical value at this time.

Participant Name:_____ **Date:** _____
Title of Study: Immune Function and Muscle Adaptation to Resistance Exercise in Older Adults
Principal Investigator: Richard Dennis, PhD
VAMC: Central Arkansas Veterans Healthcare System, 598 Version 5, Date 04-26-16

ALTERNATIVES TO PARTICIPATING IN THIS RESEARCH

The alternative to participation in this study is for you not to participate. If you chose not to participate, you could ask your Primary Care Physician for recommendations on nutrition and exercise and for an assessment of need for the TDAP vaccination. Participation is voluntary and there will be no consequences if you decide to withdraw from the research. There will be no risks associated with withdrawing from the study though we ask that you notify the study staff if you choose to withdraw.

COSTS TO PARTICIPANTS

- You will not be charged for any treatments or procedures that are part of this study. If you usually pay co-payments for VA care and medications, you will still pay these co-payments for VA care and medications that are not part of this study.
- You will not be reimbursed for expenses incurred during your participation such as travel.

PAYMENT FOR PARTICIPATION

- You will be compensated after each appointment with Kroger Gift Cards. The gift cards will be valued at $20 per research appointment. However, as stated above, at approximately 10 of the appointments, the payment is contingent upon you returning your drink calendar and used canisters.
- Two of the visits early in your participation will last approximately four hours. At these two visits you will receive $40 in Kroger gift cards.
- You will receive a $100 gift card bonus for completion of the exercise training portion of the study and a $300 gift card bonus for completing the entire study. You will receive a gift card $20 bonus for anyone you refer to the study who passes pre-screening, signs consent, and participates in the screening exam.
- The total value of the gift cards you can expect to receive for completing all aspects of the study is approximately $1,500.
- Since your compensation from VA research exceeds $600 per year, the Internal Revenue Service requires that CAVHS report this information on Form 1099-Misc. Your name and social security number may be collected on a Form W-9 and released to the Office of Accounting for this reporting.

MEDICAL TREATMENT AND COMPENSATION FOR INJURY

- According to federal regulations (Title 38 CFR17.85), the VA will provide necessary medical treatment to you as a research participant if you are injured by participation in this research project approved by the Research & Development Committee and conducted under the supervision of one or more VA employees. Except in limited circumstances, this care will be provided at this VA facility. Emergency and ongoing medical treatment will be provided as needed. This does not apply to treatment for injuries that result from non-compliance by you with study procedures.
- The VA has made no provisions for monetary compensation should an injury occur. However, you do not give up any of your legal rights and you do not release the VA from any liability by signing this form.

Participant Name:_____ **Date:** _____
Title of Study: Immune Function and Muscle Adaptation to Resistance Exercise in Older Adults
Principal Investigator: Richard Dennis, PhD
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- If you have an emergency medical problem. Call 911 and preferably go to a VA emergency room. If you go to a non-VA ER, then the expenses might not be covered by the VA.
- If you have any concerns, problems, or symptoms that you think could be related to this study, you should contact the study team. They are available the listed phone numbers 24 hours a day.
    - Dr. Richard Dennis: 501-257-3503 (office), 501-960-8024 (24-hour cell)
    - Chris Parkes: 501-257-2504 (office)
    - Physician 24-Hour Pager (Drs. Garner, Padala, Padala, and Sullivan): 501-257-1022 X 1142

PARTICIPATION IS VOLUNTARY

- Your participation is completely voluntary and you may change your mind at any time. Refusal to take part in the study will involve no penalty or loss of benefits to which you are otherwise entitled. Refusal to participate also will not affect the standard of care that you receive from the VA.
- If you withdraw from participation, please notify the study staff.
- If you withdraw, the study will confirm your wellness at least 30 days later by review of your VA medical record. No additional information about you will be collected after that date. However, any data or tissues that were collected from you prior to your withdrawal will still be used by the study.

SIGNIFICANT NEW FINDINGS

If any new findings are developed during the course of the research that may affect your willingness to continue in the research, the study team will contact you and provide you with this information so that you may reevaluate your decision to participate.

RIGHT OF INVESTIGATOR TO TERMINATE PARTICIPATION

- The study team can terminate your participation against your will. For example, this could occur if the study physician decides that it is in your best interest due to safety reasons. It could also occur if you do not adhere to the requirements of the study such as attending your visits or drinking the supplement.
- If the study team learns that you have suicidal intent, depression, intent to harm others, or other major clinical findings, the study team must act. This could include making arrangements for screening for hospital admission or notifying your primary care physician.

ADDITIONAL CONTACT INFORMATION

If at any time before, during or after your participation in this study you have questions or concerns, want to get additional information, lodge a complaint or offer your input with a person who is not part of the study team, you can contact the IRB Administrator at (501) 257-6521, the Research Compliance Officer at (501) 257-6980, or the Research and Development Coordinator at (501) 257-4816.

Participant Name:_____ **Date:** _____

Title of Study: Immune Function and Muscle Adaptation to Resistance Exercise in Older Adults

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AGREEMENT TO PARTICIPATE IN THE RESEARCH STUDY

- Dr. Dennis, Mr. Chris Parkes, or other delegated member of the study team has explained the research study to you. You have been told of the risks or discomforts and possible benefits of the study. You have been told of other choices of treatment available to you. You have been given the chance to ask questions and obtain answers.
- This informed consent form and the HIPAA authorization require your social security number because it is the means by which the VA medical records system identifies you.
- By signing this document below, you voluntarily consent to participate in this study. You also confirm that you have read this consent, or it has been read to you. You will receive a copy of this consent after you sign it. A copy of this signed consent will also be put in your medical record.
- If you wish for future contact from the study team should additional information be needed from you or for other research studies, you may indicate so by checking the box below. The contact information you provide and in your medical record will be used.

☐ Yes, I agree to future contact with the study team.

_____ _____
Signature of Participant Date Time

_____
Participant's SSN

_____ _____
Signature of Person Obtaining Consent Date

_____ _____
Signature of Investigator Date