

FULL STUDY TITLE: Validation of Body Composition Ultrasound for Identification of Sarcopenia and Cachexia in Patients with Heart Failure

SHORT TITLE: Body Composition Ultrasound for Patients With Heart Failure

Tufts Health Sciences IRB number: #13206

ClinicalTrials.gov Identifier: NCT03948776

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Study visit flow chart:

- Review eligibility criteria
- Review consent form, answer any questions
- Review pregnancy status, need for a urine test
- Sign consent

- Check height, weight
- HF etiology, duration (if relevant)
- Handgrip strength test
- 5 sit-to-stand test

Skeletal muscle ultrasound scan (portable machine)

DXA body composition scan (711 Washington Street)

If relevant, your regular cardiology clinic visit

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Study Schema

Include a diagram that provides a quick “snapshot” of the study. For examples of study schemas, refer to the [FDA and NIH’s Study Schema Examples](#) document available on the IRB website:

A. Introduction

B.1 Background and Rationale

1. *Describe the relevant prior experience and gaps in current knowledge:* We have been using the dual-energy X-ray absorptiometry (DXA) scan to measure muscle mass of patients with heart failure (HF). As the participants in these HF body composition studies are deconditioned, walking over to the DXA scan facility at 711 Washington Street can limit its use. Using a mobile hand-held ultrasound apparatus would provide a more patient-friendly method of measuring muscle mass, and we would like to generate data on its validity. We plan to compare muscle mass measurements from DXA scanning to muscle ultrasound to validate the ultrasound method.
2. *Describe any relevant preliminary data:* We have substantial experience using DXA to measure body composition in patients with HF, but no data on skeletal muscle US in this population, or the comparison between DXA and US - hence the need to for this study to generate preliminary data.
3. *Provide the scientific or scholarly background for, rationale for, and significance of the research based on the existing literature and how it will add to existing knowledge:* Cardiac cachexia, a complex wasting condition characterized by skeletal muscle loss (sarcopenia), anorexia, inflammation and abnormal biochemistry, is associated with increased morbidity and mortality for patients with systolic heart failure (HF). There are currently no nutritional or pharmacological interventions demonstrated to reverse the cardiac cachexia syndrome. We have forged a collaboration between HF cardiology and nutrition specialists at Tufts Medical Center to develop methods for body composition assessment in end-stage systolic HF patients receiving left ventricular assist devices (LVADs). Our preliminary data demonstrates that as many as half of end-stage systolic HF patients have significant sarcopenia at the time of LVAD implantation and that skeletal muscle mass improves in the first six months of LVAD support. We have also identified mechanistic contributions with patients who are sarcopenic at the time of LVAD implantation having higher resting energy expenditure and greater levels of inflammation, as compared to patients without sarcopenia. Serum metabolomics identified lower levels of the branched-chain amino acids (BCAAs) valine, leucine, and isoleucine in sarcopenic patients, with restoration of BCAA levels at three months after LVAD implantation.

Having demonstrated that sarcopenia can be reversed with LVAD implantation for patients with end-stage HF, the next step is to determine how early sarcopenia onset occurs within the natural history of systolic HF and develop an effective intervention for patients with less advanced HF. It is likely that an optimal intervention to reverse skeletal muscle mass in patients with HF will require elements of muscle substrate provision, anti-inflammatory activity and a pro-anabolic stimulus, and will probably be implemented early in the muscle loss trajectory. DXA is not an ideal technique for measuring changes in skeletal muscle mass during a sarcopenia reversal clinical trial because it is not widely available across medical centers. We also recognize that to bring sarcopenia diagnosis and treatment to the wider population of patients with systolic HF we must develop a method for inexpensive, bedside quantification of skeletal muscle mass to replace the current use of dual-energy X-ray absorptiometry (DXA). Therefore we seek to determine the utility of skeletal muscle ultrasound (US) as a novel method for sarcopenia diagnosis in patients with heart failure, given its

promising data in elderly patients with sarcopenia. Takai et al. (2014) compared skeletal muscle mass measurements by ultrasound to those acquired by DXA scan in 77 elderly subjects. They generated a regression equation using several anatomical ultrasound muscle thickness measurements to predict muscle mass measured by DXA. Ultrasound measurements of skeletal muscle have been evaluated in 2 systematic reviews (Nijholt 2017, English 2012) and have shown good performance for the prediction of lean mass. We hypothesize that DXA measurements of appendicular lean mass (ALM) will show adequate agreement with skeletal muscle US in systolic HF patients for deployment in our future HF body composition studies.

4. *Describe the relevance and usefulness of the objectives:* Measuring muscle mass will allow us to identify patients with HF who are experiencing muscle wasting. Comparing DXA scan and ultrasound measurements will demonstrate the validity of ultrasound method as a primary method for measuring muscle mass. The use of muscle ultrasound as a portable and non-ionizing screening method furthers our efforts to pursue effective therapies for cardiac cachexia.
5. *Specify whether or not this is the first time the study drug, device, or intervention/procedure will be used in humans. If there has been experience with the study drug, device, or intervention/procedure in humans, detail the experience to date:* or N/A, this is not the first time the study drug, device, or intervention/procedure will be used in humans
6. Is there an active control group?
 Yes No Yes No

B.2 Risks to Subjects

1. *List the reasonably foreseeable risks, discomforts, hazards, and/or inconveniences to the subjects related to their participation in the research, including risk of unintentional loss of confidentiality. Include a description of the probability, magnitude, duration, reversibility, and potential consequences of the risks. Consider physical, psychological, social, legal, and economic risks:* This study carries minimal risk but no direct benefits to the study participants.

Risk Assessment:

- Physical risk: Very low radiation exposure from the DXA scan (4 μ Sv). Dizziness or fatigue from 5 sit-to-stand test.
 - Psychological risk: There is no anticipated risk.
 - Social risk: There is no anticipated risk.
 - Economic risk: There is no anticipated risk. The study participants will not be reimbursed for travel. We will conduct study activities during participants' routine clinical visits.
2. *State which study interventions may have unknown risks:* or N/A
 3. *State which study interventions may have risks to an embryo or fetus (if a subject is or becomes pregnant) or to a nursing infant of a study subject:* The DXA scan has an effective radiation dose of 4 microsieverts to the whole body. The risks of this radiation dose include inducing cancer or genetic disorders in a fetus. The DXA dose is such that these risks are small by comparison with the natural incidence of these conditions: the amount of radiation obtained in 1 day from natural background radiation is 5-8 μ Sv and the amount obtained during a round-trip flight from NY to LA is approximately 60 μ Sv. Pregnant women and sexually active women who are not currently using an active form of contraception will be excluded from the study. or N/A
 4. *Describe risks to people other than the participating subject, e.g., risks to family members, friends, others or risks to the community:* or N/A
 5. Are there any risks to study investigators or staff performing the study procedures due to research with high risk populations (e.g. prisoners, intravenous drug users, patients with major psychiatric issues, etc.):?

Yes No Yes No

B.3 Potential Benefits to Subjects

1. Describe the potential benefits that individual subjects may experience from taking part in the research. Include the probability, magnitude, and duration of the potential benefits: There are no direct benefits to individual subjects; however, subjects will obtain information regarding their body composition, which they may find interesting.

Note: Payments and incentives are not considered benefits in the IRB's risk-benefit assessment; payment and incentives should be addressed in the payment section.

2. Check if there is no direct benefit.
3. Describe any benefit to the population from which the subject is drawn: This study will determine if the use of the hand-held ultrasound is comparable to that of the DXA scan. Current AHA LVAD Body Composition subjects must walk or be wheel-chaired to the HNRCA at 711 Washington Street to undergo the DXA scan. If this study proves the ultrasound applicable for muscle mass measurements, it will provide a less strenuous method of measuring muscle mass for the Body Composition Study. or N/A
4. Describe any benefit to science, society, and humanity in general: This study will validate the applicability of ultrasound muscle thickness measurements as a method to evaluate muscle mass. This will provide the cardiology community with a quicker, non-intrusive, patient-friendly method of measuring muscle mass in this patient population. or N/A

B.4 Alternatives

1. Describe alternatives to participating in this research study (e.g. to decide not participate in the study, alternative treatments, no treatment (palliative care), etc.): Subjects can decide not to participate in the study.
2. Describe the standard clinical care that may be an alternative: or N/A
3. Describe how the subject can receive the research procedures/drug/device used in this study in a non-research setting: or N/A

C. Objectives

1. Describe the purpose, specific aims, or objectives of the study (i.e. the reason for performing the study in terms of the scientific question to be answered): The primary objective of this study is to validate the use of ultrasound muscle thickness measurements to determine muscle mass. The secondary aim of this study is to use accurate muscle mass measurements to categorize patients as cachectic or sarcopenic.

Note: Specify which are the primary or secondary aims or objectives of this study as applicable. The primary objective is the main question. Secondary objectives are goals that will provide further information for the study.

D. Enrollment and Withdrawal

D.1 Inclusion Criteria

1. Describe the criteria that define who will be **included** in the study as a numbered list:
2. Inclusion criteria:
 1. Cohort A: Healthy volunteers (who may be employees)
 - 18+ years
 - No history of heart failure
 - Not pregnant
 - Willing to take a urinary pregnancy test if there is a possibility of pregnancy
 - Able to freely provide informed consent

2. Cohort B: Participants in the LVAD (left ventricular assist device) body composition study (#12026) who consent to undergo skeletal muscle ultrasound the same day as an LVAD body composition study visit that already includes the DXA and handgrip strength procedures

- Meet the eligibility criteria outlined in study #12026

3. Cohort C: Patients with heart failure, an LVAD or heart transplantation

- 18+ years
- Not pregnant
- Willing to take a urinary pregnancy test if there is a possibility of pregnancy

D.2 Exclusion Criteria

1. Describe the criteria that define who will be **excluded** in the study as a numbered list:

2. Exclusion criteria:

1. Patients requiring temporary mechanical circulatory support
2. Pregnant women, or women who report there is a possibility they could be pregnant and decline to complete a pregnancy test

3. Describe in detail how the eligibility criteria will be assessed and satisfied (e.g., medical record review, physical examination): **The eligibility criteria will be assessed by medical record review.**

4. State who will determine eligibility. Note that those who are designated to determine eligibility must have appropriate training, expertise, and oversight, for example a physician PI or Co-I on a biomedical study: **Dr. Amanda Vest will determine eligibility.**

5. Can study subjects participate in another research study while participating in this research study:

Yes No

D.3 Withdrawal of Subjects

1. Describe anticipated circumstances under which subjects will be withdrawn from the research without their consent: **If a subject behaves erratically or is extremely difficult for research staff to work with, they will be withdrawn from the study without their consent.**

2. Describe procedures that will be followed when subjects withdraw or are withdrawn from the research, including the possibility of partial withdrawal from study intervention with continued data collection: Participation in this study will last for only one day, approximately 2 hours of study activity in total. If a participant wishes to withdraw part-way through the study procedures, they are at liberty to do and no further data will be collected.

3. Describe any necessary safety precautions to be applied to subjects who withdraw or are withdrawn (tapering drug doses, evaluative x-ray, etc.): or N/A

D.4 Recruitment and Retention

D.4.1 Local Recruitment Methods

Describe the following attributes of the recruitment plan for the local Tufts site:

1. When, where, and how potential subjects will be recruited: **Recruitment will be from the list of subjects who are actively participating in, as well as subjects who have completed, the AHA LVAD Body Composition study. Recruitment of healthy individuals will be from hospital and research staff. Recruitment of other HF/VAD/Transplant patients will be from a list of Tufts Medical Center patients with heart failure, with a VAD or anticipating VAD implantation, and our heart transplant recipients.**

a. If potential subjects will be **recruited by telephone**, describe how many times the research team will attempt to call / leave a voice message: **N/A**

- i. Check to confirm that a script for **both** the telephone conversation and the voice message is included with the submission.
 - b. When subjects respond to recruitment material, describe the information that will be provided to them about the study and the information that will be collected from subjects (e.g. name, telephone number, etc.). Describe also, how many times you will attempt to respond to call the subject back / leave a voice message: **N/A**
 - i. Check to confirm that a script for **both** the telephone conversation and the voice message is included with the submission.
2. Source of subjects (for example, patient population, local community, etc.): **Patient population and local Tufts Medical Center community are the sources of subjects.**
3. Methods that will be used to identify potential subjects: **Inpatient and outpatient clinical lists, PI knowledge of outpatient clinic schedule.**
4. If print and media advertisements will be used, specify when, where, how long and frequency of the advertisements that will be published/aired: or N/A
 - a. Check to confirm that any necessary permission will be obtained for posting/airing these (for example, permission to post a flyer on a bulletin board).
5. If recruitment material is being mailed or otherwise distributed, submit the proposed material and describe where/how the distribution list will be obtained: or N/A
6. Describe how the recruitment methods described will be effective in attracting the targeted subject population: **N/A**

D.4.2 Study-Wide Recruitment Methods

Is this a multicenter study where subjects will be recruited by methods not under the control of the local Tufts site (e.g., call centers, national advertisements)?

Yes No

Yes No

If Yes, respond to all of the following:

1. Methods of recruitment not under the control of the local Tufts site: **N/A**
2. When, where, and how potential subjects will be recruited: **N/A**
3. Methods that will be used to identify potential subjects: **N/A**
4. Materials that will be used to recruit subjects: **N/A**

D.4.3 Payment

Will subjects receive money, gifts, or any other incentive for participating in this study?

This does not include reimbursement for expenses, which is considered in the next section.

Yes No Yes No

If Yes, respond to all of the following:

1. Describe any proposed payment or incentive for subjects (e.g. money, gifts cards, water bottles, tote bags, pill boxes, etc.). Include a specific description of the incentive and its value both in US and local currency (if international). The payment/incentive value must not be so great that it could cause undue influence¹:
2. Payment amount:
3. How payment will be made (e.g., cash, check, Greenphire ClinCard):
4. To whom payment will be made (subject, parent [which one], legally authorized representative):
5. Payment schedule:

¹ **Undue influence**, often occurs through an offer of an excessive or inappropriate reward or other overture in order to obtain compliance. For example, an investigator might promise psychology students extra credit if they participate in the research. If that is the only way a student can earn extra credit, then the investigator is unduly influencing potential subjects. If, however, she offers comparable non-research alternatives for earning extra credit, the possibility of undue influence is minimized.

- a. *When payment will occur:*
- b. *The payment schedule (amount at each time point), including details about the payment schedule and amount for subjects who withdraw or are withdrawn from the study:*

D.4.4 Reimbursement

Will subjects be reimbursed for their expenses, such as travel, parking, meals, or any other study related costs?

Yes No Yes No

E. Costs to Subjects

Does the research involve any costs to subjects?

Yes No Yes No

F. Study Design

F.1 Study Timelines

1. *Describe the duration of an individual subject's participation in the study:* one day, maximum 2 hours participation
2. *Describe the duration anticipated to enroll all study subjects at the Tufts study site:* 1 year
3. *Describe the estimated date for investigators to complete this study (complete primary analyses):* December 2019
4. *Describe the study procedures that will be accomplished at each study visit:* At each study visit, the subject will undergo a whole-body DXA scan and will undergo an A-mode ultrasound at 7 anatomical landmarks on the dominant side, using the BodyMetrix Pro ultrasound (Intelamatrix, Brentwood, CA).

F.2 Procedures

1. Is there a placebo control arm?
 Yes No Yes No
2. *Provide a description of all research procedures being performed as follows:*
 - a. *How individuals will be screened for eligibility. Specify screening that will take place prior to informed consent and screening that will take place after informed consent:*
 - Cohort A: Healthy volunteers (who may be employees)
 - Potential participants will be asked to confirm age >18 and no history of heart failure
 - Arrangements will be made for a urinary pregnancy test if there is a possibility of pregnancy
 - Cohort B: Participants in the LVAD (left ventricular assist device) body composition study (#12026) who consent to undergo skeletal muscle ultrasound the same day as an LVAD body composition study visit that already includes the DXA and handgrip strength procedures
 - Will be screened at the time of setting up a research study visit for #12026
 - Cohort C: Patients with heart failure, an LVAD or heart transplantation
 - Will be screened for eligibility based upon the weekly clinic list of upcoming heart failure, LVAD and transplantation patients with clinical outpatient visits to south 6 at Tufts Medical Center
 - b. *Procedures being performed to monitor subjects for safety or to minimize risks:*
Risks and their mitigation strategies are as follows:

- DXA low dose radiation – female patients will be asked if there is a possibility of pregnancy and required to complete a urine pregnancy test if any possibility present.
 - Loss of confidentiality – participants will be labeled by a study number and identified by their initials or study number on all research records. Research records will be stored on networked Tufts MC computers with password protection.
 - Dizziness or fatigue from 5 sit-to-stand test – patients will complete a safety screen consisting of one trial movement from the sitting to standing position. If they experience dizziness or fatigue they will not be allowed to proceed with the 5 sit-to-stands test.
 - No known risks of handgrip strength or skeletal muscle ultrasound.
 - c. *All drugs and devices used in the research, their regulatory approval status, and the purpose of their use:* There is no drug or device intervention. The ultrasound device, used for body composition imaging, is called the BodyMetrix BX 2000 Pro device and received 510(k) FDA clearance in 2009.
 - d. *The source records that will be used to collect data about subjects. (Attach all surveys, scripts, and data collection forms.):* Data collection form attached.
3. *Describe the following concerning pregnancy testing and birth control:*
 - a. *What type of pregnancy testing and how frequently will be conducted on women of reproductive potential. If testing will not be conducted provide the reason:* Urinary pregnancy test will be performed for women who state that they could be pregnant.
 - b. *What birth control methods **women** of reproductive potential will be instructed to use. If women will not be instructed about acceptable methods of birth control, clarify why:* None. It is only necessary to check that a female participant is not pregnant on the day of the DXA scan.
 - c. *What birth control methods **men** of reproductive potential will be instructed to use. If men will not be instructed about acceptable methods of birth control, clarify why:* None, not required for this study.
 4. *Specify which procedures, tests, visits, etc. described above are part of usual standard of care at Tufts and which are performed solely for research purposes:* The visit to the hospital is standard of care, but none of the study activities (DXA, ultrasound, handgrip strength, 5 sit-to-stand test) are standard of care.
 5. *Specify which tests are routinely performed for clinical care, but are providing data for the research, and which tests are only performed for research purposes:* None.

F.3 Evaluations

Will you perform any laboratory tests for this study?

Yes No Yes No

F.4 Collection and Storage of Human Biological Specimens (Tissue Banking)

Will biological specimens be stored for **future, unspecified**, research?

Yes No Yes No

G. Ethics and Protection of Human Subjects

G.1 Informed Consent Process

Will subjects be required to provide informed consent?

Yes No Yes No

If **Yes**, respond to all of the following:

1. *Where the consent process will take place (e.g. a private clinic room):* In a private room either in cardiology clinic (south 6), the CTRC, or a Tufts cardiology inpatient area (CCU, Pratt 8, North 6).

2. *Anticipated amount of time a potential subject will have to make a decision about participation in the study:* **At least 1 hour.**
3. *Processes to ensure ongoing consent throughout the study:* **N/A – study participation is one day only.**
4. *Check to confirm you will follow “[SOP: Informed Consent Process for Research \(HRP-090\)](#)”.*
*If **not**, answer all of the following:*
 - a. *Role of each research team member involved in the informed consent process (please note, for a biomedical study, a physician PI or Co-I should perform the informed consent process with subjects. A study coordinator may assist with this process; however, the PI or Co-I should be present to discuss the study with the subject and answer any questions, and the PI or Co-I should sign the ICF documenting that s/he has performed the informed consent process with the subject):*
The PI will perform the informed consent process, and will be responsible for explaining the study and answering questions.
 - b. *Steps that will be taken to minimize the possibility of coercion or undue influence:* **Ensure potential participants are aware that study enrollment is optional and unrelated to their standard medical care.**
 - c. *Steps that will be taken to ensure subjects’ understanding:* **We will review the study and answer all questions before offering the opportunity to sign consent.**
5. *Check to confirm that Non-English speakers will be enrolled using interpreters and IRB approved Short Forms per the [IRB’s Short Form policy](#). If IRB approved Short Forms will not be used, describe which languages the consent will be fully translated into, who will conduct the consent interview, use of interpreters, use of IRB approved translated documents, etc.:*
6. *If non-English speakers are not eligible (excluded from enrollment) for this study, provide the ethical and scientific justification, including whether this would be equitable. For example, if non-English speakers are eligible for the study and could potentially benefit from participation, it would not be equitable to exclude them:*
Refer to the [IRB Short Form Policy](#) on the IRB website for information about enrolling non-English speakers including how to reach medical interpreters.
7. *Check to confirm you will follow “[SOP: Written Documentation of Consent \(HRP-091\)](#)”.* *If **not**, describe how consent will be documented in writing:*
8. *Check to confirm you will follow “[SOP: Remote Consent Process \(HRP-092\)](#)” if there is ever a situation where consent will **not** be obtained in person. If you will follow a different process if there is ever a situation where consent will **not** be obtained in person, describe:* or N/A.

G.2 Waiver or Alteration of Consent Process

This applies for studies where informed consent will not be obtained, required information will not be disclosed, or the research involves deception.

1. Is a waiver or alteration of the consent process being requested for this study?
 Yes **No** **Yes** **No**
2. Is a waiver of the consent process being requested for parents for research involving children?
 Yes **No** **Yes** **No**
3. Is a waiver of the consent process for planned emergency research being requested?
 Yes **No** **Yes** **No**

G.3 International Research

Refer to the IRB’s [International Checklist](#) and [International Guidance](#) and include all relevant information described in those documents in this protocol: **N/A**

Data and specimens should be stored in a secure location only accessible by the research team. The PI must ensure that study documents are stored in a manner that protects the privacy of subjects and the confidentiality of study data.

1. *State where the study records, both electronic and/or paper documents including signed ICFs/assent forms, will be retained during the study (state the location for original document plus any copies that are made, e.g., if a copy of the ICF will be retained in the subject's medical record):*
2. *State where study records will be retained when the study has been closed (long-term storage):*
3. *State who, in addition to the research team, will have access to the study files, data, and/or specimens:*

4. *Explain how data and/or specimens will be transported (e.g. fax, mail, delivery, email, etc.):*
5. *Explain how data and/or specimens will be coded. Specify if there is a key to the code that matches the subjects' study identification number with their name and who, in addition to the research team, will have access to it:*
6. *Explain whether confidential genetic information will be collected from subjects:* Yes N/A
7. *Explain whether audio/videotapes and/or photographs of subjects could potentially identify the study subject. If so, indicate who will have access to (be able to view) these item, in addition to the research team, and how long the videotapes or photographs will be retained for the study and what the plan is for their destruction:* Yes N/A
8. *Check to confirm that study records will be retained for the timeframe described in the record retention policy of the "[SOP – Records Retention Timeframe – Investigators](#)". If they will not, describe the record retention plan for this study:*
9. *Check to confirm that you will follow the "[Confidentiality and Data Security Guidelines for Electronic Research Data](#)" for electronic data. If not, describe how your plan differs from these guidelines:*
10. *A Certificate of Confidentiality will be issued (for NIH studies) or obtained:* Yes N/A
CoCs protect the privacy of research subjects by prohibiting disclosure of identifiable, sensitive research information to anyone not connected to the research except when the subject consents or in a few other specific situations. NIH funded researchers are automatically issued a CoC through their award. Other Department of Health and Human Services (HHS) agencies issue CoCs to researchers they fund. Researchers not funded by HHS can apply to NIH or the FDA as appropriate to request a CoC for HHS-mission relevant research, i.e., research involving collection of information that, if disclosed, could have adverse consequences for subjects or damage financial standing, employability, insurability, or reputation. For more information, refer to [NIH's Certificates of Confidentiality Kiosk](#).

G.5 Screening Data Collection Form/Screening Log

This section specifically refers to data collected about potential subjects who are screened, but have not signed consent, for example potential subjects whose medical record is reviewed to see if they are potentially eligible, potential subjects who respond to a telephone screening call where the research team records information about the potential subject, etc. In this section "Screening Data / Screening Log" refers to any form of data collection on potential subjects who have not yet signed consent. For more information, refer to https://privacyruleandresearch.nih.gov/clin_research.asp.

Will a screening data/screening log be used in this research study?

Yes **No** **Yes** **No**

If **Yes**, respond to all of the following:

1. *Check to confirm you have submitted the Screening Data Collection Form / Screening Log to the IRB.*
2. *Review the following and provide information about the Screening Data / Screening Log and how it will be used (check only one):*
 - a. *De-identified Screening Log will be provided to and/or viewed by the Study Sponsor (the log does not record any [HIPAA identifiers](#) or contain protected health information (PHI)).*
 - i. *Explain how the Screening Log will be "distributed to" or viewed by the study Sponsor, i.e., how the Screening Log be e-mailed, sent to and /or viewed by the study Sponsor: N/A, no sponsor*
 - b. *Identifiable Screening Log that will **not** be distributed or viewed outside of the institution (although the Screening Log will record [HIPAA identifiers](#), the Screening Log will **not** leave the institution.)*

- i. *Specify the identifiers that will be collected (e.g. date of admission or clinic visit, medical record #, and reason the person was not eligible for the study):*
- c. *Identifiable Screening Log that will be distributed or viewed outside of the institution. Consider whether these identifiers could be removed from the Screening Log. It might be possible to eliminate HIPAA identifiers or use a screened subject identifier code and maintain a separate key to the code so no PHI will leave the institution.*
If it is necessary to include HIPAA identifiers in the screening log, address the following:
 - i. *The rationale for including HIPAA identifiers in the Screening Log:*
 - ii. *A plan for protecting the privacy and confidentiality of screened subjects. Screened subjects might or might not be enrolled in the research study, and since screened subjects will not have consented to the use of their PHI for research purposes, it is especially important to protect their privacy and confidentiality. The plan should include keeping identifiers to a minimum, and keeping the Screening Log in a secure location (password protected computer location only accessible by the research team or a locked file cabinet in a locked office, only accessible by the research team):*

Note: A Screening Data Collection Form / Screening Log that contains identifiers and/or PHI must NOT be sent to the study Sponsor UNLESS the IRB has granted a waiver of consent/authorization for this component of the study (or unless the investigator has obtained IRB approved consent and research authorization from each study subject whose name is on the log.)

G.6 Provisions to Protect the Privacy Interests of Subjects

1. *Describe the steps that will be taken to protect subjects' privacy interests (e.g. ensuring that discussion of the study will take place in a private area where subjects cannot be overheard):* **The consent interview will take place in a private room either in the outpatient HF clinic, CTRC or in an inpatient cardiology area at Tufts Medical Center. Family will be present whenever possible.**
2. *Describe the steps that will be taken to make the subjects feel at ease with the research situation in terms of the questions being asked and the procedures being performed. "At ease" does not refer to physical discomfort, but the sense of intrusiveness a subject might or might not experience in response to questions, examinations, and procedures (e.g. ensuring that subjects are comfortable with the research team members performing the study procedures):* **Patients will have at least 1 hour to review the study documents and consider whether they wish to participate, and potentially as long as several weeks, depending upon the scheduling of their Tufts visits. Study participation will be entirely optional and it will be emphasized that participation is unrelated to their other clinical care.**

G.7 Provisions to Monitor the Study to Ensure the Safety of Subjects

1. *Describe the plan to periodically evaluate the data regarding both harms and benefits to assess subject safety as follows:*
 - a. *The data that will be reviewed, including safety data, untoward events, and efficacy data:* **The study subject will be monitored for discomfort during the study visit and will be accompanied by a research team member who will assist with mobility and help to prevent falls. There are no medically anticipated immediate adverse effects of either a whole-body DXA scan (which involves low-dose radiation equivalent to a chest X-ray) or muscle ultrasound (which is non-ionizing).**
 - b. *Who will review the data:* **Not applicable. No safety monitoring data will be collected.**
 - c. *How the safety information will be obtained and documented (e.g., case report forms, by telephone calls with participants, printouts of laboratory results, etc.):* **Not applicable.**
 - d. *The frequency of data collection, including when safety data collection starts:* **Not applicable.**
 - e. *The frequency or periodicity of review of cumulative data:* **Not applicable.**
 - f. *The statistical tests for analyzing the safety data to determine whether harm is occurring:* **Not applicable.**

g. Any conditions that trigger an immediate suspension of the research or other action for the research:

Not applicable.

The plan might include establishing a data monitoring committee which addresses all the above.

2. Describe the entity responsible for monitoring the data, and their respective roles (e.g., the investigators, the research sponsor, a coordinating or statistical center, an independent medical monitor, a Data and Safety Monitoring Board (DSMB) /Data Monitoring Committee (DMC), and/or some other entity, and the timeframe for reporting events to this entity: **Not applicable.**
3. A copy of the DSMB/DMC Charter if the study is enclosed with the submission: Yes N/A

G.8 Vulnerable Populations

If the research involves individuals who are vulnerable to coercion or undue influence, describe the rationale for their inclusion and the additional safeguards included to protect their rights and welfare.

1. Can or will pregnant women be enrolled?
 Yes No Yes No
2. Can or will the research involve neonates of uncertain viability or non-viable neonates?
 Yes No Yes No
3. Can or will subjects who are not yet adults (neonates, children, teenagers) be enrolled?
 Yes No Yes No
4. Can or will minors who are:
 - i) married, widowed, divorced; or
 - ii) the parent of a child; or
 - iii) a member of any of the armed forces; or
 - iv) pregnant or believes herself to be pregnant; or
 - v) living separate and apart from his/her parent or legal guardian, and is managing his/her own financial affairsbe approached for study participation for either themselves or their child?
 Yes No Yes No
5. Can or will wards of the state and/or children at risk of becoming wards of the state be enrolled (this includes foster children or any child that is in state custody)?
 Yes No Yes No
6. Can or will cognitively impaired adults (adults with impaired-decision making capacity) or adults who may lose the capacity to consent be enrolled?
 Yes No Yes No
7. Can or will prisoners be enrolled?
 Yes No Yes No
8. Can or will students and/or employees be enrolled in this research?
 Yes No
 Yes No
If Yes, respond to all of the following:
 - a. Justification for specifically targeting recruitment efforts to enroll students and/or employees: **They will obtain information regarding their body composition that they may find interesting.**

- b. *How potential coercion will be eliminated:* The PI will make it very clear that participation is voluntary and the PI will not directly ask employees to participate.
- c. *Recruitment methods to be applied specifically to students and/or employees. If the same recruitment methods previously described in the protocol will be used, then state that:* Any student or employee interested in participating should email Dr. Vest regarding their interest. The PI will not directly solicit any employee to participate.
- d. *Additional safeguards included to protect the rights and welfare of students and employees:* The CVC research manager will verify with interested employees that they understand participation in the study is voluntary and that actions made towards participating were voluntary.
- e. *Protections to ensure that a subject's decision about participation and/or early withdrawal from the study will not affect his/her status as a student or employee:* The informed consent form states that participation and/or early withdrawal from the study will not affect a subject's status as a student or employee.
- f. *Check to confirm that you have submitted a letter from the appropriate institutional official (e.g., Department Chair, Dean, Vice-President) who oversees the students and/or employees attesting to the fact that the employee's or student's participation in the research is acceptable and that coercion has been minimized.*

H. Adverse Event Monitoring

H.1 Definitions

Define adverse events (AEs), serious adverse events (SAEs), and unanticipated problems for your study:

Adverse event (AE):

- 1) A new event which was not pre-existing at initial study drug administration.
- 2) A pre-existing event which recurs with increased intensity or increased frequency subsequent to study drug administration.
- 3) An event which is present at the time of study drug administration which is exacerbated following initial study drug administration.

Serious Adverse Event (SAE):

- 1) Death
- 2) Life-threatening adverse drug experience
- 3) Inpatient hospitalization or prolongation of existing hospitalization (for > 24 hours)
- 4) Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- 6) Important Medical Event (IME) that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon medical judgment, it may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Unanticipated problems

- 1) Any experience when, based upon medical judgment, it may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

H.2 Reporting Procedures

1. Describe the protocol-specific reporting procedures, including who will be responsible for each step (e.g., PI, Data Coordinating Center, Medical Monitor), which forms should be completed, timeframes for reporting, how reports will be distributed, and what follow-up is required: Any events, although not anticipated, will be reported to the IRB.
2. Include specific details of reporting procedures for:

- a. *Deaths, life-threatening events, pregnancies:* Any events, although not anticipated, will be reported to the IRB.
- b. *Other SAEs:* Any events, although not anticipated, will be reported to the IRB.
- c. *Other AEs:* Any events, although not anticipated, will be reported to the IRB.
- d. *Other UPs:* Any events, although not anticipated, will be reported to the IRB.

Ensure that the reporting procedures meet the reporting requirements of the FDA, NIH, OHRP, sponsor, study leadership and any other regulatory body that applies to the study, as applicable.

H.3 Reportable New Information

Check to confirm that reportable new information will be reported to the IRB per the Tufts Health Sciences IRB's [Reportable New Information policy](#). If your reporting plan to the IRB differs from the IRB's policies, please describe it in detail or specify where this information is in the protocol:

I. Statistical Considerations

I.1 Study Endpoints

1. *Describe the primary and secondary study endpoints:*

Primary DXA endpoint: fat free mass (FFM) measured by DXA

Primary ultrasound endpoint: FFM measured by BodyMetrix ultrasound

2. *Describe any primary or secondary safety endpoints:* N/A

I.2 Statistical Analysis

1. *Describe the statistical analyses that will be performed for this study:* Bland-Altman plot with bias and precision statistics to define the limits of agreement for FFM measured by DXA and ultrasound techniques.
2. *Provide a power analysis:* We previously showed good correlation between DXA and deuterium methods of FFM measurement in 8 patients with HF. Therefore we are aiming for a minimum enrollment of 30 subjects (10 per subgroup) and a maximum target of 60 subjects total.

I.3 Number of Subjects

1. *Specify the number of subjects to be enrolled in total across all sites:* 60 or N/A this is not a multicenter study.
2. *Specify the number of subjects to be enrolled at the Tufts site. Subjects who sign an ICF are considered "enrolled". For studies that have a separate screening ICF, this number is the number of subjects who sign a screening ICF:* 60
 - a. *Provide the rationale for enrolling this number of subjects at the Tufts site:* We plan to recruit a minimum of 30 subjects (10 per subgroup) and a maximum of 60 subjects total.
 - b. *Estimate the number of subjects expected to be enrolled at the Tufts site (i.e. sign the screening or study ICF) as well as the number needed to complete the study at the Tufts site:* 60
 - c. *If a large number of withdrawals and/or dropouts is expected, explain why:* N/A

I.4 Data Management

1. *Describe the data analysis plan, including descriptions of the data:* Bland-Altman plot with bias and precision statistics to define the limits of agreement for FFM measured by DXA and ultrasound techniques. For skeletal muscle ultrasound to be considered a valuable technique for assessment of cachexia/sarcopenia, we would require the mean differences between the US and DXA measurement methods to be less than +/- 3, which is in line with our validation of DXA measurement of fat-free mass using the deuterium reference technique.
2. *Provide a power analysis:* See above

3. Describe the steps that will be taken to secure the data (e.g., training, authorization of access, password protection, encryption, physical controls, certificates of confidentiality, and separation of identifiers and data) during storage, use, and transmission: The data will be stored only on Tufts MC networked folders with password protection and accessed within accessed-controlled academic hospital areas.
4. Describe any procedures that will be used for quality control of collected data: Review of data by PI
5. Describe how data and specimens will be handled study-wide as follows:
 - a. What information will be included in that data or associated with the specimens: Subject number, sex, age, weight, body mass index, heart failure status.
 - b. Where and how data or specimens will be stored: N/A
 - c. How long the data or specimens will be stored: N/A
 - d. Specify who will have access to the data or specimens: Research team members only
 - e. Specify who is responsible for receipt or transmission of the data or specimens: N/A
 - f. Specify how data and specimens will be transported: N/A
 - g. Specify the plan for study data retention and storage (accounting for research team turnover): The data will be stored for at least 7 years after completion of the study.

I.5 Randomization

Will subjects be randomized?

Yes No Yes No

J. Drugs or Devices

1. Will the research involve drugs?

Yes No

Yes No

2. Will the research involve devices?

BodyMetrix Pro body composition ultrasound device

Yes No

If **Yes** to either, respond to all of the following:

1. Who on the research team, in addition to the Principal Investigator, will be accountable for drug(s)/device(s): Joronia Chery, Rani Kuttab, Rachel Porth (all team members) are all trained on the BodyMetrix Ultrasound device and accountable for secure storage
2. Who will interface with the pharmacy (drugs) or sponsor (devices): Amanda Vest interfaces with device vender (Intelametrix, Brentwood, CA) for any ultrasound device questions. There is no device sponsor or drug.
3. If pre-printed orders will be created to obtain study drug(s) from the pharmacy, describe the procedures for reviewing and verifying the accuracy of the pre-printed orders prior to their being implemented: or N/A, there are no pre-printed orders
4. If computerized order sets are created and/or infusion devices need to be programmed to administer an investigational drug, indicate the mechanism to pre-review and verify their accuracy, including who will be involved in this process from the research team, pharmacy, and nursing: or N/A, there are no computerized orders sets and/or infusion devices.
5. The study drug, device, or procedure (including beneficial health care procedures) will be available to subjects after participation in the study: Yes N/A
6. There are medications or other substances that should not be taken while participating in the study. A list of these are incorporated into the ICF a subject handout: Yes N/A
7. Handouts or instructions sheets that will be given to subjects on how to administer study drug(s) or use study device(s) have been submitted to the IRB: Yes N/A

K. Study Administration

K.1 Setting

1. Describe the sites / locations where your research team will conduct the research: South 6 cardiology clinic, CTRC, cardiology inpatient areas e.g. CCU, Pratt 8, North 6.
2. The research will take place at an international site, and the [International Guidance](#) and [International Checklist](#) were utilized: Yes N/A

K.2 Registration

1. Describe the steps the research team will take to ensure that a subject is appropriately enrolled or registered in the study prior to receiving any study intervention (e.g. describe and submit any protocol eligibility checklist that will be used, specify who on the research team will confirm eligibility and that consent was documented, etc.): N/A

K.3 Resources Available

1. Describe the roles/tasks of each research team member here (or alternatively, you may submit any current Delegation of Authority Log you may have which already has this information completed):
Joronia Chery: Research Coordinator - arranges study visits, accompanies subjects to DXA, performs ultrasound
Rani Kuttab: Research Coordinator - arranges study visits, accompanies subjects to DXA, performs ultrasound
Amanda Vest: PI – performs consent, oversees research activities, performs ultrasound, performs analyses
Rachel Porth: Co-I – arranges study visits, performs ultrasound, performs analyses
2. Describe the qualifications (e.g., training, experience) of the PI and research team to perform their roles. Provide enough information for the IRB to determine the PI and research team are qualified to conduct the proposed research. Alternatively, you can submit the current CVs for the research team instead: CVs submitted
3. Describe the coverage plan to address any issues (including subject safety issues) that occur while the PI is away and/or unavailable. The research team member designated to serve as the acting PI in the PI's absence should have similar training and expertise as the PI: No study visits will be performed when the PI is unavailable.
4. Describe the process to ensure the research team members have adequate oversight and are adequately trained regarding the protocol, study procedures, and their roles and responsibilities: PI meets with the study team weekly to review enrollment, visits, data and subject safety.
5. Medical or psychological resources that subjects might need, such as for emergencies or medical issues, are available for the study: Yes N/A

K.4 IRB Review

1. Check to confirm that an appropriate IRB registered with the OHRP, will review and approve this study.
2. Check to confirm that any amendments to the protocol or informed consent documents will be reviewed and approved by the IRB prior to use, unless required to eliminate an apparent immediate hazard to subjects.

K.5 Multi-Site Research

Is this a multi-site study where Tufts is the sponsor, primary grant recipient, or coordinating site?:

Yes No Yes No

K.6 Community-Based Participatory Research

Note: "Community-based Participatory Research" is a collaborative approach to research that equitably involves all partners in the research process and recognizes the unique strengths that each brings. Community-based Participatory

Research begins with a research topic of importance to the community, has the aim of combining knowledge with action and achieving social change to improve health outcomes and eliminate health disparities.

Can or will this study involve community-based participatory research?

Yes No Yes No

K.7 Sharing Results with Subjects

Will results (overall study results or individual subject results, such as results of investigational diagnostic tests, genetic tests, or incidental findings) be shared with subjects or others (e.g., the subject's primary care physician or the subject's treating physician)?

Yes No Yes No

If Yes, respond to all of the following:

1. *Rationale for sharing these results:* To inform subjects of their current body composition and engage their interest in participation.
2. *How results will be shared:* A paper sheet (template provided) reporting body composition testing by the two methods.
3. *For individual subject results, specify if subjects have the option to opt-in or opt-out of receiving these results or allowing these results to be shared with others:* Subjects can opt out of receiving their body composition results by verbal request.
4. *Any referral policies (i.e. for confirmation of any individual subject results):* The PI will review any very abnormal body composition results with the Registered Dietician on the heart transplant team who oversees each subject's nutritional consultation during standard of care and can advise on nutritional approaches towards weight gain or loss.
5. *Check to confirm that testing of research specimens is being conducted in a laboratory certified (CLIA-approved) to conduct diagnostic testing. If patient-specific research results are reported from the laboratory and those results will or could be used for the diagnosis, prevention, or treatment of any disease or impairment, or the assessment of the health of human beings, the laboratory must be [CLIA certified](#).*
6. *If the research tests are experimental or of unknown or unproven clinical significance and the results will be provided to the source individual or physician or placed in the source individual's medical record, provide the rationale for this:* The body composition DXA and ultrasound techniques are both considered experimental and are not standard of care. However we believe that the results will be of interest to participating subjects and are enthusiastically received in our other IRB-approved body composition study.

L. References

Provide a list of references for all citations included in the protocol

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2. English C, Fisher L, Thoires K. Reliability of real-time ultrasound for measuring skeletal muscle size in human limbs in vivo: a systematic review. *Clin Rehabil.* 2012;26:934–944.
3. Takai Y, Ohta M, Akagi R, Kato E, Wakahara T, Kawakami Y, Fukunaga T, Kanehisa H. Applicability of ultrasound muscle thickness measurements for predicting fat-free mass in elderly population. *J Nutr Health Aging.* 2014;18:579–585.
4. Abe T, Loenneke JP, Young KC, Thiebaud RS, Nahar VK, Hollaway KM, Stover CD, Ford MA, Bass MA, Loftin M. Validity of ultrasound prediction equations for total and regional muscularity in middle-aged and older men and women. *Ultrasound in Medicine & Biology.* 2015;41:557–564.

5. Connolly B, MacBean V, Crowley C, Lunt A, Moxham J, Rafferty GF, Hart N. Ultrasound for the assessment of peripheral skeletal muscle architecture in critical illness: a systematic review. *Critical Care Medicine*. 2015;43:897–905.
6. Paris MT, Mourtzakis M, Day A, Leung R, Watharkar S, Kozar R, Earthman C, Kuchnia A, Dhaliwal R, Moisey L, Compher C, Martin N, Nicolo M, White T, Roosevelt H, Peterson S, Heyland DK. Validation of Bedside Ultrasound of Muscle Layer Thickness of the Quadriceps in the Critically Ill Patient (VALIDUM Study): A Prospective Multicenter Study. *Journal of Parenteral and Enteral Nutrition*. 2016;20:1–10.
7. Abe T, Fujita E, Thiebaud RS, Loenneke JP, Akamine T. Ultrasound-Derived Forearm Muscle Thickness Is a Powerful Predictor for Estimating DXA-Derived Appendicular Lean Mass in Japanese Older Adults. *Ultrasound in Medicine & Biology*. 2016;42:2341–2344.
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9. Nijholt W, Scafoglieri A, Jager-Wittenaar H, Hobbelen JSM, van der Schans CP. The reliability and validity of ultrasound to quantify muscles in older adults: a systematic review. *J Cachexia Sarcopenia Muscle*. 2017;8:702–712.
10. Abe T, Loenneke JP, Thiebaud RS. The use of ultrasound for the estimation of muscle mass: one site fits most? *J Cachexia Sarcopenia Muscle*. 2017;9:213–214.
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