Human Subjects Research Protocol

The Common Human Subjects Protocol Cover Form **must** be completed and **attached** to the front of this form. This Protocol form should be completed for any human subjects research proposal that does not have a specific "protocol," such as a grant application. This form must be submitted along with a copy of the complete grant proposal and all the information in this form **must** be consistent with that proposal. This protocol form, once IRB approved, will be the working protocol for that research. **When completing this document, do not refer to page numbers within your grant**. If revisions are necessary during the course of the research, amendments should refer to this protocol form, not the grant proposal. Enter responses for all sections. Check N/A if the section does not apply.

PROTOCOL SUMMARY

Project Title:	Protocol Version Date:
Neuromuscular Electrical Stimulation in Heart Failure Patients to Improve Functional Recovery Following Hospitalization (NeuHF-Recover).	11/30/2023

Principal Investigator: Sherrie Khadanga

Grant Sponsor: Department of Medicine Grant Number: Not applicable
(For grants routed through UVM, indicate the OSP Proposal ID # located at the top of the OSP Routing Form)

Lay Language Summary: *(Please use non-technical language that would be understood by nonscientific IRB members to summarize the proposed research project. The information must include: (1) a brief statement of the problem and related theory supporting the intent of the study, and (2) a brief but specific description of the procedure(s) involving the human subjects. Please do not exceed one single-spaced 8 ½ X 11" page.)*

Heart failure (HF) is the leading cause of hospitalization among adults in the US,[1,2] with patients with preserved ejection fraction (HFpEF), defined as EF>50% and patients with moderate to reduced ejection fraction (<50%)Approximately 20% of HFpEF patients will be re-admitted within 30 days and >50% within 1 year, with increased risk of mortality.[2,3] While most research has focused on HF with reduced EF<40% (HFrEF), patients with HFpEF have higher rates of outpatient and ED visits.[3] Despite high rates of mortality and health care utilization, there is no proven treatment for HFpEF and, as readmissions and ED visits suggest, there is gap in their transition of care post hospitalization.

Chronic fatigue, exercise intolerance and an inability to perform activities of daily living are hallmark symptoms of HF that negatively impact quality of life and prognosis.[4]Physical disability is exacerbated by hospitalization, in which bed rest can cause acute muscle loss and further disability.[5,6] The importance of hospital-acquired disability is underscored by the fact that reduced mobility at hospital discharge is predictive of 30 d readmissions.[7] Even after acute HF symptoms resolve, many patients experience deficits in strength, balance and mobility and some never regain baseline function.[6] Exercise training is beneficial in improving physical function in these patients, but classical exercise training is difficult during the acute post-phase discharge and cardiac rehabilitation is not covered for HFpEF patients.[6,8] Many HF studies have focused on guideline directed medical therapy, however, few have focused on rehabilitation following hospitalization.[8]

A home based exercise intervention following hospital discharge may improve physical functional recovery, but there are numerous barriers to home exercise in HF patients. Neuromuscular electrical stimulation (NMES) offers a potential solution to these barriers, as it confers an exercise training effect without the physical requirements of traditional exercise. NMES is an inexpensive, safe, FDA- approved intervention which allows non-volitional initiation of muscle contractions that mimic resistance or aerobic type exercise, leading to training responses similar to traditional exercise.[9] In older adults with chronic

disease, including HF patients, NMES improves muscle strength, but its ability to improve physical function is equivocal.[10] Additionally, these studies were small and mostly performed in the outpatient setting with stable HFrEF patients without recent hospitalization.[11] Thus, whether NMES is effective in HFpEF and HFrEF patients at improving functional recovery following the acute disabling effects of hospitalization is unclear.[9-11]

The purpose of this phase 4 randomized controlled trial is to establish the feasibility and efficacy of NMES administered to the quadriceps muscles to improve early functional recovery in older heart failure patients recently hospitalized for HF. Functional status will be objectively measured via the 6-minute walk test (6MW) and Short Physical Performance Battery tests (SPPB). Based on our pilot results in patients undergoing cardiac surgery, we hypothesize that the use of NMES will improve functional recovery.[12] Successful completion of this study will provide seminal data regarding the utility of NMES to improve functional capacity following hospitalization in heart failure patients, which may have implications for both readmission and long term prognosis

PURPOSE AND OBJECTIVES

Purpose: *The importance of the research and the potential knowledge to be gained should be explained in detail. Give background information.*

As the US population ages, there has been a rise in patients experiencing heart failure and, in turn, hospitalizations and readmissions.[2,3] Focus has been placed on transitional care services for medical and surgical treatments, with little attention on physical rehabilitation services, despite the fact that patients prioritize this as an outcome of their treatment and that physical disability increases risk of complications and readmission.[5-7] After hospitalization, HFpEF patients are severely deconditioned, but HFpEF is not a qualifying diagnosis for outpatient cardiac rehabilitation (CR). Our intervention aims to overcome this gap in rehabilitative care early after hospital discharge to improve functional recovery.

NMES is an innovative modality to bridge the critical gap in transition of care for these patients. Numerous trials have found that NMES improves muscle strength in ***stable*** HFrEF patients, but its effects on physical function are equivocal and only 1 small study examined NMES in clinically stable outpatient HFpEF patients.[8-10] ***To our knowledge, the proposed study would be the first to investigate the utility of NMES to improve functional recovery in*** heart failure ***patients following hospitalization.*** Our rationale for targeting this period is based on our work in cardiac surgical patients, where functional gains during recovery after hospitalization were substantial, but also because regaining functional capacity during this period is important for long-term disability and clinical outcomes.[11,12]

Results from this study can advance our existing treatment of heart failure in several ways. First, it will provide evidence of a novel rehabilitation intervention to improve functional status after a disabling event, such as hospitalization. With the exception of our own work, virtually no studies have examined NMES in the acute, post-discharge setting. Secondly, it may improve health outcomes given that hospital-acquired disability/decondition increases risk of complications and readmissions.[11,12] Vermont's rural environment makes it challenging for patients to access medical care and rehabilitation. Our proposed study is ***conceptually innovative*** in developing a transitional rehabilitative intervention to address an important sector of older cardiac patients prone to hospital-acquired disability and rehospitalization. At this time, HFpEF patients are not eligible for CR and HFrEF patients must wait 6 weeks before CR enrollment, therefore, NMES can provide a portable, high value, home-based intervention to aid in the recovery of physical function for heart failure patients recently discharged from the hospital.. Few studies have assessed the utility of NMES to improve functional recovery following an acute, disabling event.[8-10,13] If successful, our data could ***advance a new model for early post-hospitalization rehabilitation***.

References*. Include references to prior human or animal research and references that are relevant to the design and conduct of the study.*

References

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13. Karavidas A, Driva M, Parissis JT, et al. Functional electrical stimulation of peripheral muscles improves endothelial function and clinical and emotional status in heart failure patients with preserved left ventricular ejection fraction. *Am Heart J*. 2013;166(4):760-767.
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15. Brochu M, Savage P, Lee M, et al. Effects of resistance training on physical function in older disabled women with coronary heart disease. *J Appl Physiol (1985)*. 2002;92(2):672-678.
16. McHorney CA, Ware JE Jr, Lu JF, Sherbourne CD. The MOS 36-item Short-Form Health Survey (SF-36): III. Tests of data quality, scaling assumptions, and reliability across diverse patient groups. *Med Care*. 1994;32:40–66
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Objectives: *Clearly state the primary and secondary objective(s) of the study.*

Patients with heart failure have high rates of hospitalization and mortality. Unfortunately, there is lack of evidence based therapies for this cohort. While exercise improves clinical status in patients with HFpEF, these patients are often severely deconditioned and have difficulty engaging in traditional exercise programs. This deconditioning typically evolves during hospitalization, when disease exacerbation and treatments conspire with physical inactivity to cause skeletal muscle deconditioning. Failure to remediate lost functional capacity contributes to worsened symptoms and greater risk for disability. Neuromuscular electrical stimulation (NMES) of the lower extremity has proven to be an alternative to physical exercise and can serve as a bridge for heart failure patients to regain strength and improve functional status following hospitalization. The proposed studies will assess the efficacy of a novel rehabilitation intervention to improve functional recovery after a disabling event specifically hospitalization in older heart failure patients.

Primary Aim: Determine whether NMES of the lower extremity musculature improves physical functional recovery in older heart failure patients recently hospitalized for congestive heart failure. We *hypothesize* that NMES will improve recovery of physical function compared to the control.

Secondary Aim: Define the effects of NMES on self-reported physical function and quality of life at 4 weeks from baseline. We *hypothesize* that NMES will improve quality of life and self-reported physical function compared to the control.

METHODS AND PROCEDURES

Study Design: *Describe the research design, including a description of any new methodology and its advantage over existing methodologies.*

Study design: We will use a randomized-controlled trial design. Patients admitted for heart failure will be recruited and randomized to NMES or control for 4 weeks following hospital discharge. Patients will be stratified by sex and age. Baseline testing will occur prior to discharge and consist of functional assessment by 6MW and SPPB and completion of 2 questionnaires regarding quality of life and physical function (Kansas City Cardiomyopathy questionnaire {KCCQ} and (Medical Outcomes Study Short Form-36 {MOS SF-36}). After completion of the 4 week intervention period, patients will undergo Post-Testing which will be identical to Baseline testing.

Inclusion/Exclusion Criteria: Patients will be recruited if they: 1) have clinical diagnosis of heart faliure being actively managed during hospitalization, 2) live within 30 miles of UVMMC and are between 50-90 years of age. Patients will be excluded if they have: 1) severe dementia/alzheimer's disease 2)an active malignancy, excluding non-melanoma skin cancer or low-grade prostate cancer under active surveillance; 3) exercise-limiting vascular or neuromuscular disease; 4) body mass index ≥40 kg/m^2 or 5*) an existing lower extremity blood clot or implantable cardioverter-defibrillator (ICD) or pacemaker (PPM).[14] *The last criteria is a contraindication for NMES and we will withdraw patients if they develop a blood clot or receive an ICD or PPM.

Randomization and blinding: Patients will be randomized prior to hospital discharge to NMES or control using Pocock and Simon's covariate-adaptive randomization for which sex and age will be stratified. The unblinded project manager will train patients to use NMES device and oversee them during the intervention. The PI and co-I will be blinded to treatment assignment.

Interventions:
Usual care: Patients will not receive an NMES device. We opted not to use "sham" stimulation (eg, low-intensity stimulation below the threshold to initiate contraction) lessen the chance that patients may increase stimulation to produce contractions if there is perceived benefit. Patients will be contacted weekly to assess overall recovery. As there is currently no standard of care rehabilitation for these patients following discharge and NMES does not have demonstrated benefits, our study meets the requirements for clinical equipoise.

NMES: NMES will be carried out bilaterally on the quadriceps using a portable stimulator. Two adhesive electrodes will be placed to the anterior surface of each thigh. Symmetrical, biphasic pulses (400 μs duration at 25 Hz) will be used, with a duty cycle of 25% (10 s on, 30 s off). Patients will be trained to conduct NMES sessions and will select stimulation intensities sufficient to cause visible muscle contractions below their pain threshold. Training in the use of the NMES device will begin prior to hospital discharge. After discharge, NMES sessions will occur 5 d/wk once per day for 45 min per occasion (5 min low-intensity warm-up, 40 min higher-intensity stimulation) for 4 wks. This program is meant to mimic an aerobic-type exercise stimulus and similar to prior protocols. Daily logs and weekly phone calls will be used to monitor compliance to maximize intervention fidelity with overall compliance measured using the device software.

Outcomes: The primary outcome is 6MW. Functional capacity measures and quality of life measures will be obtained at baseline (prior to hospital discharge) and at 4 weeks.

1. Baseline characteristics including age, body mass index, length of hospital stay, medications, and smoking status
2. Functional Capacity measures:
    a. 6-MW test is a well-validated method to assess functional capacity in patients with cardiac disease and shows convergent validity with other indices of physical function The test will be conducted under standardized conditions, as described by us.[11,15] Distance walked (m) will be the primary outcome.
    b. SPPB will be measured, as it is a widely used, easy to measure index of physical function in older adults. Thus, it provides context for the severity of disability in our population and the modifying effects of NMES for comparison to other studies.[11]
3. Quality of Life measures:
    a. Self-reported physical functioning assessment using the Medical Outcomes Study Short Form-36 (MOS SF-36) survey questionnaire (0-100 scale) with 100 representing excellent physical functioning[16]
    b. Kansas City Cardiomyopathy questionnaire[17]
4. Hospital readmission and Emergency Department visits within 3 months
5. Activities of Daily Living measures:
    a. Lawton Brody ADL questionnaire
    b. Katz Index of Independence in Activities of Daily Living

Procedures: *Describe all procedures (sequentially) to which human participants will be subjected. Identify all procedures that are considered experimental and/or procedures performed exclusively for research purposes. Describe the types, frequency and duration of tests, study visits, interviews, questionnaires, etc. Include required screening procedures performed before enrollment and while on study. Please provide in table, list or outline format for ease of review. (describe and attach all instruments)*

Note: A clinical research protocol may involve interventions that are strictly experimental or it may involve some aspect of research (e.g., randomization among standard treatments for collection and analysis of routine clinical data for research purposes). It is important for this section to distinguish between interventions that are experimental and/or carried out for research purposes versus those procedures that are considered standard therapy. In addition, routine procedures performed solely for research purposes (e.g., additional diagnostic/follow-up tests) should be identified.

All of the procedures and interventions on volunteers recruited for these studies are carried out solely for research purposes, as none are part of standard therapy in heart failure patients.

Physiological Testing (Discharge and 1 month post discharge)

SPPB will be measured, as described by us (1), as this assessment is prognostic for functional competence and mortality in cardiac surgical patients (2). This measure takes ~5 min to perform and is comprised of: 5 repeated chair stands, balance testing (3 tasks each 10 s long) and a 4 meter walk. As increasing SPPB score in the first month post-discharge in a sample of elderly patients with diverse clinical backgrounds was associated with lower risk for rehospitalization and death (3), improvements in, or maintenance of, this metric would provide strong evidence for the clinical utility of NMES. We have experience with this measure in cardiac populations (4).

6 MW was developed to assess cardiopulmonary fitness in patients with lung and cardiac disease

(5), but has been used widely to assess disability in older adults (6) and is the most common metric used when seeking FDA approval for interventions to improve physical function. We have experience with this measure in heart failure patients (7).

Treatment phase

NMES will be carried out bilaterally on the quadriceps using a portable stimulator (EMPI Continuum). Two adhesive electrodes will be affixed to the anterior surface of each thigh: ~1 cm distal to the inguinal crease and ~5 cm proximal to the patella, just lateral to the midline of the thigh to assure that it does not interfere with incisions for vein harvest. Symmetrical, biphasic pulses (400 μs duration at 25 Hz) will be used, with a duty cycle of 25% (10 s on, 30 s off). Patients will be trained to conduct NMES sessions and will select stimulation intensities sufficient to cause visible muscle contractions below their pain threshold. Training in the use of the NMES device will begin prior to day of discharge. . This training will consist of one session per day of ~15 min to familiarize the volunteer with the unit and the exercise/contraction stimulus. Upon discharge, NMES sessions will occur 5 d/wk once per day for 45 min per occasion (5 min low-intensity warm-up, 40 min higher-intensity stimulation) for 4 wks. This program is meant to mimic an aerobic-type exercise stimulus (8) and has been shown in heart failure patients to have functional benefits over a similar treatment period (9, 10). We acknowledge that the NMES training load is substantial, but have modeled this program on others that have shown morphological and functional effects in heart failure patients (11). At this exploratory stage, we feel that it is essential to use a stimulus that affects muscle size and function, with future studies modifying the NMES dose to establish a threshold that elicits a training effect with the highest subject compliance rate. Daily logs and weekly phone contacts will be used to track compliance, and compliance will be covertly monitored using the device software.

Control patients will not receive an NMES device. We chose not to utilize a control NMES intervention (eg, stimulation below threshold to elicit contraction) to mitigate the possibility that patients may increase stimulation to produce muscle contractions if there is perceived benefit. Rigorous control over the NMES stimulus is preferable to controlling for any effects of sub-threshold, cutaneous electrical stimulation. Patients will be contacted weekly to assess their recovery and discuss issues related to general health to equate the degree of interaction with study personnel to that of the NMES intervention group.

Quality of Life measures: will be assessed with the following questionnaires which will be obtained at baseline (discharge) and 1 month following discharge

a. Self-reported physical functioning assessment using the Medical Outcomes Study Short Form-36 (MOS SF-36) survey questionnaire (0-100 scale) with 100 representing excellent physical functioning
b. Kansas City Cardiomyopathy questionnaire

Activities of Daily Living measures:

a. Lawton Brody ADL questionnaire
b. Katz Index of Independence in Activities of Daily Living

References cited above:

1. Ades, P. A., Savage, P. D., Cress, M. E., Brochu, M., Lee, N. M., and Poehlman, E. T. (2003) Resistance training on physical performance in disabled older female cardiac patients. *Med Sci Sports Exerc* **35**, 1265-1270
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For research involving survey, questionnaires, etc.: *Describe the setting and the mode of administering the instrument and the provisions for maintaining privacy and confidentiality. Include the duration, intervals of administration, and overall length of participation. (describe and attach all instruments)*

☐ ***Not applicable***

We will assess physical functionality/quality of life with the MOS-SF36 questionnaire and KCCQ. This questionnaire takes about ~10 min to complete and will be completed at Discharge and 4 wk Post-hospitalization discharge

Statistical Considerations: *Delineate the precise outcomes to be measured and analyzed. Describe how these results will be measured and statistically analyzed. Delineate methods used to estimate the required number of subjects. Describe power calculations if the study involves comparisons. Perform this analysis on each of the primary and secondary objectives, if possible.*

Statistical Analysis:

Primary outcome is the 6MW. Other outcomes include SPPB, KCCQ and MOS SF-36 questionnaire results and subsequent ER visits and hospitalizations. The two experimental groups will be compared on baseline demographic characteristics using one-way Analysis of Variance (ANOVA) for continuous measures and chi-square tests (or Fisher's Exact Test) for categorical variables. Our primary outcome is to assess changes in physical function (specifically 6MW) between study groups to test whether NMES improves functional recovery from discharge to 4 weeks. We will use analysis of covariance to model primary and secondary outcomes, as this is the preferred model to assess data in pre-post RCTs. In this model, the 4-week post-discharge value is the dependent variable and the value at hospital discharge is a covariate. Sex interactions for response to NMES will be examined. We will assess QOL by questionnaires to determine if NMES improves patient-reported QOL vs. usual care. Clinical and other factors that may modify the response to NMES (eg, length of stay, etc) can be included in the model to control for potential confounders that might differ by group in the event that randomization fails to equate groups.

Sample Size Calculation:

The proposed sample of 60 participants is based on having sufficient power to calculate differences in our primary outcome (6MW) between the control condition and the intervention and accommodating for potential drop outs (20%) from the study.[11] Power is estimated to be 80% to detect a difference in the change in 6MW between the 2 groups at the $p<0.05$ level. These estimates are based on data from a meta-analysis of RCTs of NMES in *stable* patients with chronic heart failure which detected a difference of 47 m between NMES group vs placebo as well as our pilot data of CABG patients, where patients randomized to NMES increased 6-MW distance 73 m further than controls.[11] We assume a 6-MW distance of 250 ± 60 m (mean ± SD) at hospital discharge in both groups. Additionally, we have reduced the improvement in 6-MW distance in the NMES group by ~30% to 50 m (6-week post-discharge NMES: 250 ± 60 m vs. Control: 300± 60 m) to be conservative. This magnitude improvement in 6-MW is similar to meaningful changes found in 6-MW performance in older adults with mild- to moderate mobility disability undergoing home-based strength training (47 m) and is twice the minimal clinically significant difference in patients with cardiac disease following CR (25 m).[18] Therefore, we will need to recruit 60 patients with our target of 48 patients to complete the study (n=24/group), assuming a drop out of 20%. We have not performed sample size estimates for SPPB or secondary outcomes, as extrapolating the ability of NMES to affect other variables is challenging barring relevant preliminary data, particularly in *recently hospitalized* heart failure patients.

Risks/Benefits: *Describe any potential or known risks. This includes physical, psychological, social, legal or other risks. Estimate the probability that given risk may occur, its severity and potential reversibility. If the study involves a placebo or washout period, the risks related to these must be addressed in both the protocol and consent. Describe the planned procedures for protecting against or minimizing potential risks and assess their likely effectiveness. Where appropriate, discuss plans for ensuring necessary medical or professional intervention in the event of adverse effects to the subjects. Discuss the potential benefits of the research to the subjects and others. Discuss why the risks to the subjects are reasonable in relation to the anticipated benefits to subjects and others. Discuss the importance of the knowledge gained or to be gained as a result of the proposed research and why the risks are reasonable in relation to the knowledge that reasonably may result. If there are no benefits state so.*

Potential risks: Below we have highlighted those procedures/measurements that have anything greater than negligible risk to the volunteers' health for each phase of the study.

Testing: Risks associated with functional testing are minimal. All of the activities are similar to those performed during the conduct of normal daily activities. If volunteers are unable to do any of the activities because of limitations of their heart condition, they will not be required to perform them and testing will be monitored by trained personnel.

NMES intervention: NMES is a generally safe procedure, delivered in the proposed study by an FDA approved device. Although evidence is limited, some have suggested that NMES could increase the risk of DVT, which may have serious health consequences. However, several published reports show that NMES significantly reduces the risk of developing deep vein thromboses (DVT) (1) and we will actively exclude any individual with a known coagulopathy. Because of the location of the stimulating electrodes (upper leg), the risk of NMES dislodging a DVT is likely minimal. We will also exclude any volunteers that currently have an implanted cardiac defibrillator or pacemaker, as this is contraindicated for NMES use (1). Patients may experience some painful muscle contractions as they first adjust the stimulus to a tolerable level, which can be quickly corrected by reducing the stimulation intensity. After treatment, muscles soreness may occur. The level of fatigue and/or soreness, however, will be similar to that which occurs following a standard exercise training session and should dissipate over time as the volunteer's muscles become accustomed to the electrically-stimulated contractions (ie, they become trained).

Benefits: The direct benefit of the research to volunteers is minimal. NMES may improve skeletal muscle structure or function and, in turn, improve physical functional capacity. Because of this, patients may experience improved physiological capacity, which could reduce disability. If we find that NMES has beneficial effects on physical function, further research and application of the technique to heart failure patients may assist in the development of more effective transitional rehabilitative care approaches to mitigate long-term functional morbidity.

References cited above:

1. Houghton, P. E., Nussbaum, E. L., and Hoens, A. M. (2010) Electrophysical agents. Contraindications and precautions: an evidence-based approach to clinical decision making in physical therapy. *Physiother Can* **62**, 1-80
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Therapeutic Alternatives: *List the therapeutic alternatives that are reasonably available that may be of benefit to the potential subject and include in the consent form as well.*

☐ ***Not Applicable***

There are no alternative rehabilitation regimens during the early, post-hospitalization period for heart failure patients.

Data Safety and Monitoring: *The specific design of a Data and Safety Monitoring Plan (DSMP) for a protocol may vary extensively depending on the potential risks, size, and complexity of the research study. For a minimal risk study, a DSMP could be as simple as a description of the Principal Investigator's plan for monitoring the data and performance of safety reviews or it could be as complex as the initiation of an external, independent Data Safety and Monitoring Board (DSMB). The UVM/UVM Medical Center process for review of adverse events should be included in the DSMP.*

Drs. Khadanga and Toth will monitor the safety of the research procedures for this study. We have not set up a formal safety committee for several reasons. First, the PIs and the investigative team have a long history of performing the measurements proposed in this proposal. The procedures carry relatively low risk to the volunteers. Second, because of the small number of patients and track record of performing these procedures, it is highly unlikely that we will need to "stop" the study or significantly

alter the procedures. If any problems/unanticipated events arise related to the NMES intervention, Dr. Khadanga will determine the nature of the problem and its relatedness to the NMES intervention and decide whether continued participation in the study is in the best interest of the patient. As detailed above, however, NMES is FDA-approved for this indication and we have taken precautions to minimize the potential for adverse effects.

Adverse Event and Unanticipated Problem (UAP) Reporting: *Describe how events and UAPs will be evaluated and reported to the IRB. All protocols should specify that, in the absence of more stringent reporting requirements, the guidelines established in the Committees on Human Research "Adverse Event and Unanticipated Problems Reporting Policy" will be followed. The UVM/UVM Medical Center process for review of adverse events and UAPs to subjects or others should be included in the DSMP.*

The PIs or the study coordinator (Jason Rengo) will monitor the safety of the research procedures/interventions for this study. Mr. Rengo or Dr. Khadanga will be available on-site for all assessments that may pose safety concerns for volunteers. Additionally, subjects will be contacted weekly to review device use and any difficulty or issues that may have occurred since the last contact. General muscle soreness is expected in some subjects and will not be considered an adverse event. Subjects reporting severe muscle discomfort limiting daily activity or other potential adverse events (i.e. skin irritation) will be instructed to discontinue device use pending further review. In this context, study personnel will be readily available to monitor volunteer safety throughout the study. If an event occurs that affects participant safety, Mr. Rengo will alert Dr. Khadanga, who will adjudicate the event with respect to its severity, expectedness and relatedness to participation in the study. Because numerous studies in our laboratories and others have demonstrated the safety of this regimen of testing in patients from with a broad range of clinical backgrounds (eg, heart failure patients, cancer patients, advanced-stage, knee OA patients; healthy elderly), we expect minimal problems related to testing or the intervention. Considering the low risk nature of these studies, we have not incorporated "stoppage criteria" for the overall study. Instead, Dr. Khadanga will decide whether an individual participant should continue with the study following occurrence of any adverse events or unanticipated problems, taking into consideration what is in the best interest of each individual patient.

Adverse events will be reported by one of 3 mechanisms. First, the joint University of Vermont/University of Vermont Medical Center (UVMMC) Committee for Human Subject Research Adverse Event Reporting Document. These reports will be sent to the office of the Committee for Human Research in the Medical Science (CHRMS) within 2 days of the event. Reporting any adverse events will be the responsibility of the PIs. The CHRMS will make a determination as to whether additional reporting requirements are indicated. Additionally, the UVMMC Patient Safety Reporting system (SAFE), which may be initiated by health care center staff or study personnel. These forms will be forwarded within 3 days to the PI, UVMMC Risk Management Office, CHRMS and other appropriate agencies, as indicated by the nature of the report. Reviews of protocol specific adverse events will be performed no less than annually. Additionally, any adverse event that occurs will be forwarded to the PIs for reporting to the Human Subject Research Protection Office within 1 week of occurrence. Of note, these protections against risk include both physical risks to the volunteers, as well as risks associated with any breach in confidentiality.

On an annual basis, Drs. Toth and Khadanga will assess data being gathered and safety of volunteers to assess the pattern or frequency of events to identify occurrence of any event or problem that alters the safety profile of the procedures being performed. The exception would be occurrence of a serious adverse event or unanticipated problem that necessitates re-evaluation of the expected risk of the study procedures at an earlier time point. Additionally, they will evaluate data collection and storage to ensure the confidentiality of data and quality. Each of these evaluations will be followed by reports of study progress and patient safety to the University of Vermont CHRMS via yearly progress reports.

Withdrawal Procedures: *Define the precise criteria for withdrawing subjects from the study. Include a description of study requirements for when a subject withdraws him or herself from the study (if applicable).*

Volunteers will be withdrawn if the research team, clinician and/or safety officer feels that further participation in the study or performance of any procedure associated with this study would, in any way, put the volunteer at undue risk or not be in their best interest. Moreover, volunteers may be withdrawn if s/he fails to attend scheduled visits or do not comply with instructions from research staff.

Sources of Materials: *Identify sources of research material obtained from individually identifiable human subjects in the form of specimens, records or data. Indicate whether the material or data will be obtained specifically for research purposes or whether use will be made of existing specimens, records or data.*

An individual research record will be kept on each volunteer in compliance with HIPAA standards. This record will contain identifying data, demographic information and results from all clinical research measurements and evaluations. The results of all testing will be kept confidential. All materials gathered in conjunction with the proposed studies will be used for research purposes only and will be available only to research personnel working on these studies, who have obtained proper training in human subjects research and privacy protection.

DRUG AND DEVICE INFORMATION

Investigators are encouraged to consult the UVM Medical Center Investigational Pharmacy Drug Service (847-4863) prior to finalizing study drug/substance procedures.

Drug (s) [X] ***Not applicable***

Drug name – generic followed by brand name and common abbreviations. Availability – Source and pharmacology; vial or product sizes and supplier. If a placebo will be used, identify its contents and source. (attach investigational drug brochure)

Preparation: Reconstitution instructions; preparation of a sterile product, compounded dosage form; mixing guidelines, including fluid and volume required. Identify who will prepare.

Storage and stability – for both intact and mixed products.

Administration – Describe acceptable routes and methods of administration and any associated risks of administration.

Toxicity – Accurate but concise listings of major toxicities. Rare toxicities, which may be severe, should be included by indicated incidence. Also adverse interactions with other drugs used in the protocol regimen as well as specific foods should be noted. Address significant drug or drug/food interactions in the consent form as well. List all with above details.

Is it FDA approved: (include FDA IND Number)

1. *in the dosage form specified? If no, provide justification for proposed use and source of the study drug in that form.*
2. *for the route of administration specified? If no, provide justification for route and describe the method to accomplish.*
3. *for the intended action?*

Device (s) [ ] ***Not applicable***

Device name and indications (attach investigational device brochure)

The interventional device used in this study: EMPI Continuum complete electrotherapy system has received FDA approval (501K: K093324) for retarding disuse-related atrophy, which we believe is one of the primary mechanisms whereby HFpEF patients become more functional disabled in the early, post-hospitalization period. That is, muscle disuse secondary to limited range of motion and muscle weakness causes skeletal muscle fiber atrophy and weakness, as well as mitochondrial rarefaction and dysfunction that further impair physical fitness.

Is it FDA approved: (include FDA IDE Number)

1. *for indication specified? If no, provide justification for proposed use and source of the device.*

Yes. It is approved to mitigate muscle atrophy/dysfunction associated with muscle disuse (501K: K093324) (see Appendix 3).

Risk assessment (non-significant/significant risk) - PI or sponsor needs to assess risk of a device based upon the use of the device with human subjects in a research environment.

The device (and similar devices) has been used extensively in the orthopedic and neural rehabilitation settings by physical and occupational therapists and in numerous disease states (heart failure, chronic obstructive pulmonary disease, knee replacement) to improve muscle size and function in clinical trial settings. Thus, NMES is generally a safe modality, with a long safety record. Although evidence is limited, some have suggested that NMES could increase the risk of dislodging a DVT because of the rhythmic muscle contractions induced by the electrical stimulation. However, several published reports show that NMES significantly reduces the risk of developing DVTs. In fact, the device we are using is

FDA-approved for prevention of DVT of the calf muscles immediately following hospitalization, as it would function similar to intermittent pneumatic compression. Moreover, we will actively exclude any individual with a known coagulopathy or DVT. Because of the location of the stimulating electrodes (upper leg), the risk of NMES dislodging a DVT is likely minimal. There are also several case reports that NMES may be sensed by cardiac defibrillators as an arrhythmia, causing the device to discharge inappropriately. However, interference with ICDs mostly involved low frequency stimulation of the upper or lower back. In contrast, a more recent study has shown that higher frequency stimulation of the leg muscles does not cause electromagnetic interference with the device (1). Regardless, consistent with current clinical practice guidelines (2), we will exclude any volunteers that currently have an implanted cardiac defibrillator or pacemaker. Finally, during the first couple of NMES sessions, muscle soreness may occur, but this is comparable to what might occur with classical exercise training and dissipates over time.

Literature cited

1. Kamiya, K., Satoh, A., Niwano, S., Tanaka, S., Miida, K., Hamazaki, N., Maekawa, E., Matsuzawa, R., Nozaki, K., Masuda, T., and Ako, J. Safety of neuromuscular electrical stimulation in patients implanted with cardioverter defibrillators. *Journal of Electrocardiology* **49**, 99-101
2. Houghton, P. E., Nussbaum, E. L., and Hoens, A. M. (2010) Electrophysical agents. Contraindications and precautions: an evidence-based approach to clinical decision making in physical therapy. *Physiother Can* **62**, 1-80

SUBJECT CHARACTERISTICS, IDENTIFICATION AND RECRUITMENT

Subject Selection: *Provide rationale for subject selection in terms of the scientific objectives and proposed study design.*

Patients who are hospitalized to the Inpatient Cardiology Service for heart failure with preserved ejection fraction (HFpEF) and reduced ejection fraction (HFrEF) otherwise known as diastolic heart failure or systolic heart failure will be screened. As the US population ages, there has been a rise in patients experiencing HFpEF and HFrEF and, in turn, hospitalizations and readmissions.[1-3] Focus has been placed on transitional care services for medical and surgical treatments, with little attention on physical rehabilitation services, despite the fact that patients prioritize this as an outcome of their treatment and that physical disability increases risk of complications and readmission.[5-7] After hospitalizationheart failure patients are severely deconditioned.. Our intervention aims to overcome this gap in rehabilitative care early after hospital discharge to improve functional recovery

1. Dunlay SM, Roger VL, Redfield MM. Epidemiology of heart failure with preserved ejection fraction. *Nat Rev Cardiol*. 2017;14(10):591-602.
2. Bello NA, Claggett B, Desai AS, et al. Influence of previous heart failure hospitalization on cardiovascular events in patients with reduced and preserved ejection fraction. *Circ Heart Fail*. 2014;7(4):590-595. doi:10.1161/CIRCHEARTFAILURE.113.001281
3. Nichols GA, Reynolds K, Kimes TM, Rosales AG, Chan WW. Comparison of Risk of Re-hospitalization, All-Cause Mortality, and Medical Care Resource Utilization in Patients With Heart Failure and Preserved Versus Reduced Ejection Fraction. *Am J Cardiol*. 2015;116(7):1088-1092.
4. Aggarwal M, Bozkurt B, Panjrath G, Aggarwal B, Ostfeld RJ, Barnard ND, Gaggin H, Freeman AM, Allen K, Madan S, Massera D, Litwin SE; American College of Cardiology's Nutrition and Lifestyle Committee of the Prevention of Cardiovascular Disease Council. Lifestyle Modifications for Preventing and Treating Heart Failure. J Am Coll Cardiol. 2018 Nov 6;72(19):2391-2405
5. Reeves GR, Whellan DJ, Duncan P, et al. Rehabilitation Therapy in Older Acute Heart Failure Patients (REHAB-HF) trial: Design and rationale. *Am Heart J*. 2017;185:130-139
6. Fisher SR, Kuo YF, Sharma G, et al. Mobility after hospital discharge as a marker for 30-day readmission. *J Gerontol A Biol Sci Med Sci*. 2013;68(7):805-810
7. Reeves GR, Whellan DJ, Patel MJ, et al. Comparison of Frequency of Frailty and Severely Impaired Physical Function in Patients ≥60 Years Hospitalized With Acute Decompensated Heart Failure Versus Chronic Stable Heart Failure With Reduced and Preserved Left Ventricular Ejection Fraction. *Am J Cardiol*. 2016;117(12):1953-1958

Vulnerable Populations: *Explain the rationale for involvement of special classes of subjects, if any. Discuss what procedures or practices will be used in the protocol to minimize their susceptibility to undue influences and unnecessary risk (physical, psychological, etc.).*

X ***Not applicable***

Number of Subjects: *What is the anticipated number of subjects to be enrolled at UVM/UVM Medical Center and in the case of a multi-center study, with UVM/UVM Medical Center as the lead, the total number of subjects for the entire study.*

The proposed sample of 60 participants is based on having sufficient power to calculate differences in our primary outcome (6MW) between the control condition and the intervention and accommodating for potential drop outs (20%) from the study. We will need to recruit 60 patients with our target of 48 patients to complete the study

Inclusion/Exclusion Criteria: *Eligibility and ineligibility criteria should be specific. Describe how eligibility will be determined and by whom. Changes to the eligibility criteria at a later phase of the research have the potential to invalidate the research.*

Inclusion/Exclusion Criteria: Patients will be recruited if they: 1) have clinical diagnosis of heart failure being actively managed during hospitalization, 2) live within 30 miles of UVMMC and are between 50-90 years of age. Patients will be excluded if they have: 1) severe dementia/alzheimer's disease 2)an active malignancy, excluding non-melanoma skin cancer or low-grade prostate cancer under active surveillance; 3) exercise-limiting vascular or neuromuscular disease; 4) body mass index ≥40 kg/m^2 or 5*) an existing or history of deep vein thrombosis (DVT) or have an implantable cardioverter-defibrillator (ICD) or pacemaker (PPM).[1] *The last criteria is a contraindication for NMES and we will withdraw patients if they have an existing or history of deep vein thrombosis of the lower extremities or have an ICD or PPM

Literature cited:

1. Houghton, P. E., Nussbaum, E. L., and Hoens, A. M. (2010) Electrophysical agents. Contraindications and precautions: an evidence-based approach to clinical decision making in physical therapy. *Physiother Can* **62**, 1-80

Inclusion of Minorities and Women: *Describe efforts to include minorities and women. If either minorities or women are excluded, include a justification for the exclusion.*

Inclusion of Women

This study will include equal numbers of men and women.

Inclusion of Minorities

Every effort will be made to recruit minorities for the proposed studies. The contribution of minorities to the total population of Vermont is 3.2%, with a similar minority profile in Chittenden County (3.6%), where the University of Vermont (UVM) is located.

Inclusion of Children: *Describe efforts to include children. Inclusion is required unless a clear and compelling rationale shows that inclusion is inappropriate with respect to the health of the subjects or that inclusion is inappropriate for the purpose of the study. If children are included, the description of the plan should include a rationale for selecting or excluding a specific age range of children. When included, the plan must also describe the expertise of the investigative team in working with children, the appropriateness of the available facilities to accommodate children, and the inclusion of a sufficient number of children to contribute to a meaningful analysis relative to the purpose of the study.* ***If children are excluded*** *then provide appropriate justification. Provide target accrual for this population.*

The proposed studies will not include children because HFpEF/HFrEF is confined to the adult/ older adult population.

For protocols including the use of an investigational drug, indicate whether women of childbearing potential have been included and, if not, include appropriate justification.

Not applicable

If HIV testing is included specifically for research purposes explain how the test results will be protected against unauthorized disclosure. Include if the subjects are to be informed of the test results. If yes, include the process and provision for counseling. If no, a rationale for not informing the subjects should be included.

X ***Not applicable***

Recruitment: *Describe plans for identifying and recruitment of subjects. All recruitment materials (flyers, ads, letters, etc) need to be IRB approved prior to use.*

Patients will be recruited from the Inpatient Cardiology Service on Miller.

FINANCIAL CONSIDERATIONS

Expense to Subject: *If the investigation involves the possibility of added expense to the subject (longer hospitalization, extra studies, etc.) indicate in detail how this will be handled. In cases where the FDA has authorized the drug or device company to*

charge the patient for the experimental drug or device, ***a copy of the authorization letter from the FDA or sponsor must accompany the application. Final approval will not be granted until the IRB receives this documentation.***
There are very limited circumstances under which study participants may be responsible (either directly or via their insurance) for covering some study-related expenses. If the study participant or their insurer(s) will be billed for any portion of the research study, provide a justification as to why this is appropriate and acceptable. For example, if the study involves treatment that is documented standard of care and not investigational, state so. In these cases, the protocol and the consent should clearly define what is standard of care and what is research.

The only added cost to the volunteer is for their transportation to and from the research center for additional testing associated with these studies, as described above.

Payment for participation: *Describe all plans to pay subjects, either in cash, a gift or gift certificate. Please note that all payments must be prorated throughout the life of the study. The IRB will not approve a study where there is only a lump sum payment at the end of the study because this can be considered coercive. The amount of payment must be justified. Clarify if subjects will be reimbursed for travel or other expenses.*

☐ ***Not applicable***

We propose to compensate volunteers $200 for their participation. If volunteers do not complete the study, their compensation will be prorated accordingly.

At Initial Evaluation:	$50
Week 1 f/u phone call:	$25
Week 2 f/u phone call:	$25
Week 3 f/u phone call:	$25
Week 4 f/u phone call:	$25
Final evaluation:	$50

Collaborating Sites*. When research involving human subjects will take place at collaborating sites or other performance sites when UVM/UVM Medical Center is the lead site, the principal investigator must provide in this section a list of the collaborating sites and their Federal-wide Assurance numbers when applicable. (agreements may be necessary)*

X ***Not applicable***

INFORMED CONSENT

Consent Procedures*: Describe the consent procedures to be followed, including the circumstances under which consent will be obtained, who will seek it, and the methods of documenting consent. Specify the form(s) that will be used e.g. consent (if multiple forms explain and place identifier on each form), assent form and/or HIPAA authorization (if PHI is included). These form(s) must accompany the protocol as an appendix or attachment.*

Note: Only those individuals authorized to solicit consent may sign the consent form confirming that the prospective subject was provided the necessary information and that any questions asked were answered.

If the patient expresses interest in the study and would like more information about the study, the research coordinator or PI will contact the volunteer, explain the study and will provide a copy of the informed consent. The PI and/or the research coordinator will answer any questions by phone or in person. Moreover, the PI or the research coordinator will discuss the protocol with the volunteer at length and answer any remaining questions.

Information Withheld From Subjects: *Will any information about the research purpose and design be withheld from potential or participating subjects? If so, explain and justify the non-disclosure and describe plans for post-study debriefing.*

X ***Not applicable***

Attach full grant application, including budget information and/or any contract or draft contract associated with this application.