Protocol Title	The Impact of Lower Extremity Weight-Bearing Leg Exercise During the Pre-Ambulation Phase of Individuals Undergoing Extracorporeal Membrane Oxygenation (ECMO)
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	Institutional Email Address:
Scientific Assessment	Not required, Minimial Risk Study
ClinicalTrials.gov	NCT03135210
IND/IDE Holder	N/A.
Investigational Drug Services # (if applicable)	N/A.
Version Number/Date:	11/28/16

PROTOCOL COVER PAGE

REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?

Table of Contents

ABBREVIATIONS/DEFINITIONS

- ECMO: Extracorporeal Membrane Oxygenation
- PT: Physical Therapy

1.0 Study Intervention(s)/Investigational Agent(s)

1.1 Description:

We are conducting this study to explore the impact of closed-chain leg exercise in individuals undergoing ECMO. Closed-chain leg exercise will be completed on the MOVEO XP Platform System. Drug/Device Handling:

1.2 Biosafety: N/A

1.3 Stem Cells: N/A

2.0 Local Procedures Involved and Local Requirements

2.1 Local Procedures: N/A

2.2 Individually Identifiable Health Information: De-identified participant data will be used in the data analysis process. Individual data will be collected during scheduled physical therapy sessions and therefore a part of the subject's medical record regardless of study participation. As with any medical record information, individuals can request medical record access, in this case, all subjects will be at UMMC Fairview and will need to follow the process outlined by Fairview for such a request.

2.3 Use of radiation*: N/A*

2.4 Use of Center for Magnetic Resonance Research*:N/A*

3.0 Provisions to Monitor the Data to Ensure the Safety of Participants

3.1 Protecting Privacy: Subjects are working with physical therapy regardless of enrollment in this study. At any time they can request to stop either therapy or the study. Their medical records are secured in the Fairview system. Data extracted for study purposes is accessed by the primary therapist and de-identified prior to input into REDcap system.

3.2 Data Integrity Monitoring. N/A

3.3 Data Safety Monitoring. N/A

4.0 Data and Specimen Banking

4.1 Storage and Access: Study personnel who have completed HIPAA, CITI, and other data management training through the University of Minnesota Medical Center, Fairview and the University of Minnesota will be responsible for the collection, management, and analysis of study data.

Participants will be randomized to groups through a randomization service prior to study initiation. All participants will be assigned a subject number that will be stored on a computer at the University of Minnesota, which is

password protected. Data collected from participant's medical records will be managed exclusively by the primary therapist and the PI, and stored in a password protected data management system through Research Electronic Data Capture (REDCap), available at the University of Minnesota.

In accordance with regulations, participant records will be stored for a minimum of three years following completion of the study. After the stated timeframe and if data is no longer needed, records will be destroyed.

4.2 Data: No future use is intended, data is not banked for additional analysis.

4.3 *Release/Sharing:* Subjects are working with physical therapy regardless of enrollment in this study. At any time they can request to stop either therapy or the study. Their medical records are secured in the Fairview system. Data extracted for study purposes is accessed by the primary therapist and de-identified prior to input into REDcap system.

5.0 Sharing of Results with Participants

Please reference main protocol, section 19.0, page 14 of 16

6.0 Local Study Population

Please reference criteria found in main protocol section 9.0, page 11 of 16

7.0 Vulnerable Populations

7.1 Vulnerable Populations:

- ☐ Children
- ☐ Pregnant women/Fetuses/Neonates
- ☐ Prisoners
- ☐ Adults lacking capacity to consent and/or adults with diminished capacity to consent, including, but not limited to, those with acute medical conditions, psychiatric disorders, neurologic disorders, developmental disorders, and behavioral disorders
- ☐ Approached for participation in research during a stressful situation such as emergency room setting, childbirth (labor), etc.
- ☐ Disadvantaged in the distribution of social goods and services such as income, housing, or healthcare
- ☐ Serious health condition for which there are no satisfactory standard treatments
- ☐ Fear of negative consequences for not participating in the research (e.g. institutionalization, deportation, disclosure of stigmatizing behavior)
- ☐ Any other circumstance/dynamic that could increase vulnerability to coercion or exploitation that might influence consent to research or decision to continue in research

☐ Undervalued or disenfranchised social group
☐ Members of the military
☐ Non-English speakers
☐ Those unable to read (illiterate)
☐ Employees of the researcher
☐ Students of the researcher
☒ None of the above

7.2 Additional Safeguards: N/A

8.0 Local Number of Participants

8.1 Local Number of Participants to be Consented:

Local Number of Participants to be Consented: This initial pilot study will be conducted at the University of Minnesota Medical Center (UMMC), Fairview, and will involve 10 participants in each of the two groups (A and B). To account for attrition, 24 total subjects will be recruited; 12 per group. Approximately 3-5 patients are admitted to UMMC each month who are undergoing ECMO and could be considered for study inclusion. The study will be conducted with a goal endpoint of 1-year.

9.0 Local Recruitment Methods

9.1 Recruitment Methods: Recruitment Process: Individuals consented are those already being seen by physical therapists at UMMC, Fairview as a part of standard practice. Physical therapy delivery will either involve or not involve the Moveo XP platform system, if individuals consent to participate and based on Group assignment (A or B).

9.2 Identification of Potential Participants: Standard practice includes a physician order for inpatient physical therapy for all individuals undergoing ECMO, as well as initial medical sedation. Most of those receiving ECMO are at least partially medically sedated at the time of physical therapy initiation. Only physical therapists who are specialty-trained ICU therapists and who are a part of this project will be working with this group of patients.

Any individual who meets inclusion criteria will be considered for participation, pending their ability to follow 3/3 one-step commands, as is outlined in the ECMO Mobility Protocol listed previously. Patients will be able to self-consent once sedation is reduced. After consent, individuals will be placed into either Group A or B and progress through the protocol. Group assignments will be determined based on 24 subjects, with the number 24 put into a random letter sequence generator prior to subject recruitment.

- Physical therapists working at Fairview have legitimate access to records as a part of their employment. The off-site PI will only have access to de-identified data, not medical records.
- The physical therapist assigned to a given patient will initiate contact with patients (potential subjects).

9.3 Recruitment Materials: No recruitment materials are needed.

9.4 Payment: There is no funding or payment associated with any part of this study.

10.0 Withdrawal of Participants

Please reference main protocol, section 13.0 pages 12-13 of 16

11.0 Risks to Participants

Please reference main protocol, section 14.0, page 13 of 16

12.0 Potential Benefits to Participants

Please reference main protocol, section 15.0 page 13 of 16

13.0 Confidentiality

Please reference page 14 of main protocol, section 17.0

14.0 Provisions to Protect the Privacy Interests of Participants

Please see page 14 of main protocol, section 19.0

15.0 Compensation for Research-Related Injury

15.1 Compensation for Research-Related Injury: N/A

15.2 Contract Language: N/A

16.0 Consent Process

16.1 Consent Process (when consent will be obtained): Once subjects are removed from sedation and able to follow 3/3 one-step commands.

- Consent will occur in the hospital room of the subject. There will be no waiting period between initial consent and initiation of study.
- Ongoing verbal consent to activity will be addressed daily, when the therapist approaches a subject for scheduled therapy.
- Consent will be obtained via pre-approved form.

16.2 Non English-Speaking Participants: Any non-English speaking individual who is being treated by a physical therapist and who is undergoing ECMO treatment would be eligible for consent. As advised by IRB, a line on the consent form indicating who facilitated consent in the case of a non-English speaker, has been added.

16.3 Participants Who Are Not Yet Adults (infants, children, teenagers under 18 years of age): N/A

16.4 Cognitively Impaired Adults, or adults with fluctuating or diminished capacity to consent: N/A

16.5 Adults Unable to Consent: N/A

17.0 Setting

17.1 Research Sites: Fairview, University of Minnesota Medical Center, East Bank Hospital. Treatment and consent will occur in the hospital room of each subject.

18.0 Multi-Site Research:

N/A

19.0 Resources Available

19.1 Resources Available: Resources Available: Feasibility of subjects is dependent on the number of individuals undergoing ECMO treatment and able to provide consent. This is a pilot study.

- Research space and software is available at the University of Minnesota, Division of Physical Therapy. Data collection will be completed at Fairview, East Bank Hospital.
- All research support staff have been trained on the protocol, completed regulatory HIPAA and CITI training.

Project Proposal: 11/28/16

The Impact of Lower Extremity Weight-Bearing Leg Exercise During the Pre-Ambulation Phase of Individuals Undergoing Extracorporeal Membrane Oxygenation (ECMO)

Principal Investigator: Amanda LaLonde, PT, DPT, University of Minnesota
Co- Investigator: Eric Andersen, PT, DPT, University of Minnesota Medical Center, Fairview

Project Summary

Patients undergoing extracorporeal membrane oxygenation (ECMO) are at high risk for deconditioning and functional decline. Current research provides support for early mobilization of patients undergoing ECMO, and indicates that activity in this population is safe and feasible. The timeframe prior to mobilization depends on a number of factors, and can range significantly between different patient groups. One such factor is strength.

While active lower extremity exercise is common in the pre-ambulation phase of those receiving ECMO, the type of exercise selected varies and little is know about the benefit of weight-bearing closed chain exercise during this pre-ambulatory period. In order to evaluate this specific form of exercise, we will compare outcomes of patients who complete lower extremity exercise without loading to those who complete loaded exercises.

All participants in this study will progress through pre-existing Ambulatory ECMO Guidelines, established and currently in use at the University of Minnesota Medical Center, Fairview. Participants will be randomized into either group A or B. Group A will receive specific closed chain lower extremity squat exercises via the MOVEO XP Mobile Hi-Lo Platform System. MOVEO is an exercise leg press device. The MOVEO exercises will be added during parts C and D of the ECMO Early Mobilization Protocol listed below. Group B will progress through the ECMO Early Mobilization Protocol without the addition leg exercises on the MOVEO.

Collecting and analyzing data on weight-bearing lower extremity exercise in this patient population will allow us to obtain important information on ways to address weakness associated with ECMO treatment, particularly in those who are unable to engage in bipedal ambulation.

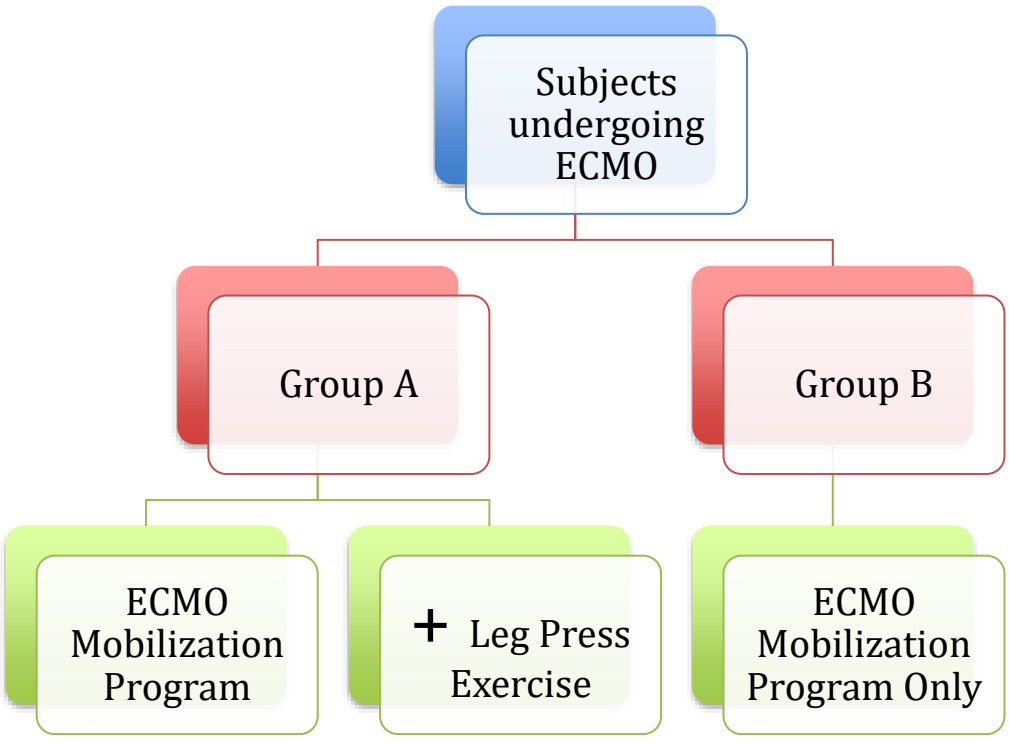
MOVEO XP Mobile Hi-Lo Platform System

Company Website:

http://www.djoglobal.com/products/chattanooga/moveo-xp

ECMO Early Mobilization Protocol:

1. **Readiness for Mobility Assessment and Protocol** (Developed by ECMO therapy specialists at the University of Minnesota Medical Center)
    a. Passive range of motion (PROM) and monitor for appropriateness of entering into the mobility program
    b. Utilization of lift equipment to sit patient at the edge of the bed or into chair to promote wakefulness, when on minimal amounts or no sedation
    c. Patient demonstrates the ability to follow 3/3 one-step commands
    d. Patient tolerates 5 minutes of lower extremity ergometer, or performs ten reps of 3 active ROM of motion exercises involving the lower extremities
    e. Sit at bedside unsupported for 5 minutes
    f. Sit<>stand and pre-gait activities (weight shifting, walking in place, etc.) directed by therapist
    g. Bed←→chair transfers (stand-pivot or squat-pivot)
    h. Walking over ground with utilization of the mobility carts



The primary aim of this study is to assess the functional impact of leg exercise during the pre-ambulation phase in patients undergoing ECMO. Outcome measures will be categorized as either functional or hospital based. Hospital measures include: Hospital days, intensive care unit days, days on ECMO, days on mechanical ventilation, length of time from physical therapy evaluation to initial ambulation, and discharge disposition. Functional outcome measures include: Leg strength, grip strength, 30-second sit to stand test, Functional Status Score for the Intensive Care Unit (FSS-ICU), and the Richmond Agitation and Sedation Scale (RASS).

Background & Significance

Typical care for persons undergoing ECMO has involved levels of medical sedation to the point of unresponsiveness to outside stimuli. Past treatment theories have identified numerous contraindications for mobilization (Hodgson et al 2014). Recent advances in ECMO cannulation site (veno-venous) now allow these patients to safely mobilize. A growing body of evidence has suggested that mobilizing while undergoing ECMO is safe, feasible and improves both medical and functional outcomes. For example, Abrams et al. (2014) found that physical therapy (PT) may increase extracorporeal gas exchange efficiency, and that patients may be earlier eligible for extubation as a result of PT. A study by Rehder et al. was suggestive of improved post-lung transplant recovery time when patients participated in active rehabilitation while on ECMO. A more recent study in 2016 by Bain et al. concluded that subjects who were ambulatory while on ECMO had significant direct medical cost reductions including total hospital cost ($60,204), post-transplant ICU cost ($104,939) and reduction in total cost compared with non-ambulatory ECMO subjects ($32,133).

Ambulation, while safe and effective, may not be feasible early on for some critically ill patients. In these cases, exercise is often a pre-ambulatory intervention. Selection and impact assessment of open versus closed chain exercise has been well documented in literature related to recovery after knee injury, but to a lesser degree in those who are immobile due to critical illness. Studies have reported knee extensor atrophy during bed rest (Bamman 2000) and functional benefit of specificity training (Morrissey, et. al 1998), yet little is known about the functional effectiveness of loaded closed chain exercises as compared to the open chain exercises in the critically ill patient population.

Coupled with known data reflective of muscle changes and strength loss with immobility (Puthucherary, et. al 2010), this study aims to broaden the treatment repertoire to include lower extremity closed chain muscle training (hip and knee extensors) along with determining the safety and feasibility of such an intervention for critically ill individuals undergoing ECMO.

Specific Aims

We are conducting this study to explore the impact of closed-chain leg exercise in individuals undergoing ECMO.

Aim 1: To determine if closed-chain leg exercise decreases the time to initial ambulation. *We hypothesize* that adding leg exercise will decrease time to ambulation.

Aim 2: To determine the impact of closed chain leg exercise on functional ability. *We hypothesize* that adding leg exercise will improve functional outcomes when added to an existing early mobilization program.

Aim 3: To determine the effect of closed chain leg exercise on hospital outcomes. *We hypothesize* that hospital related outcomes will improve when leg exercise is added to an existing early mobilization program.

Research Design & Methods

This initial pilot study will be conducted at the University of Minnesota Medical Center (UMMC), Fairview, and will involve 10 participants in each of the two groups (A and B). To account for attrition, 24 total subjects will be recruited; 12 per group. Approximately 3-5 patients are admitted to UMMC each month who are undergoing ECMO and could be considered for study inclusion. The study will be conducted with a goal endpoint of 1-year. Men and women aged 18-70 years old with refractory respiratory failure who are undergoing ECMO will participate over the duration of their ECMO treatment and hospitalization.

<u>Recruitment and Consent</u>
Standard practice includes a physician order for inpatient physical therapy for all individuals undergoing ECMO, as well as initial medical sedation. Most of those receiving ECMO are at least partially medically sedated at the time of physical therapy initiation. Only physical therapists who are specialty-trained ICU therapists and who are a part of this project will be working with this group of patients.

Any individual who meets inclusion criteria will be considered for participation, pending their ability to follow 3/3 one-step commands, as is outlined in the ECMO Mobility Protocol listed previously. Patients will be able to self-consent once sedation is reduced. After consent, individuals will be placed into either Group A or B and progress through the protocol. Group assignments will be determined based on 24 subjects, with the number 24 put into a random letter sequence generator prior to subject recruitment.

Inclusion Criteria

- Men and women 18-70 years old with refractory respiratory failure undergoing ECMO at the University of Minnesota Medical Center, Fairview.
- Able to follow 3 out of 3 one-step commands via protocol.
- Active Inpatient Physical Therapy Referral.
- ECMO delivery is veno-venous with internal jugular catheter.

Exclusion Criteria

- Femoral catheter of any kind present.
- Veno-arterial ECMO setup.
- Sedation such that self-consent is not attainable.
- Medical instability, as determined by primary critical care physician.

Overview of Protocol for Aims 1-3:

Participants in either Group A (closed chain leg exercise group) or B (open chain exercise group) will progress through the established ECMO protocol led by their physical therapist. Participating therapists have extensive experience in working with patients on the Moveo who are in the ICU. Subjects will be assisted in the supine position from their bed to the Moveo device via a lateral transfer across a slide board to facilitate ease of movement.

Those in Group A will participate in leg exercise on the Moveo during item 4d of the ECMO protocol, whereby those in Group B will complete standard exercise as listed in item 4d. Group A participants will use the Moveo until subjective report of leg fatigue. Participants will self-select the pace of their leg exercise and the primary therapist will determine guidelines for percent of body weight lifted in accordance with standard practice physical therapy. Subjects will complete 1-4 sets of up to 25 reps of the squat exercise with 2 minutes of rest between each set. Subjects will receive physical therapy 5 days/week regardless of randomization into Group A or Group B.

Data Collection for Aims 1-3: Data will be collected on Day 0 (physical therapy evaluation day), Day 5, Day 10, Day 15, Day 20, Day 30, Day 45 (if applicable), and Day of discharge. Data collected will be categorized as specific to Aim 1 (time from initial physical therapy evaluation to initial ambulation), Aim 2 (functional outcomes) and Aim 3 (hospital outcomes). Recording of physiological data including heart rate (HR), blood pressure (BP), oxygen saturation (O2), and respiratory rate (RR) will be completed by trained physical therapists involved in the protocol at the onset of, and 1-minute post-conclusion of each therapy session. Therapy sessions are to be delivered at a frequency of five sessions per week.

- Functional Outcomes
    - Leg strength as assessed by primary therapist via manual muscle test, using the Medical Research Council Sum Score (MRC Score)
    - Grip strength, as assessed by hand dynamometer, completed by primary therapist

- 30-second sit to stand, completed by primary therapist
- Richmond Agitation and Sedation Scale (RASS), as completed in medical record by primary nurse
- Functional Status Score for the Intensive Care Unit (FSS-ICU)

- Hospital Outcomes (data extraction from medical record)
  - Hospital days
  - Intensive care unit days
  - Days on ECMO
  - Days on mechanical ventilation
  - Length of time from physical therapy evaluation to initial ambulation
  - Discharge disposition- assigned a number for statistical analysis
    - Home (1)
    - Home with assistance (2)
    - Home with home therapy (3)
    - Home with outpatient therapy (4)
    - Transitional Care Unit (5)
    - Acute Inpatient Rehabilitation (6)
    - Long-term acute care hospital (7)
    - Long-term care setting (8)
    - Transfer to outside hospital (9)

- Physiological Monitoring: Monitoring physical therapists have extensive experience in mobilizing patients in the ICU, including those with arterial lines and on ventilation, as is standard practice for ICU therapy.
  - Respiratory rate (RR) via Drager Ventilators
    - Evita Series or Infinity Series
  - Oxygen (SpO2) and heart rate (HR)
    - Spacelabs Ultraview SL2700 (regular monitor)
    - Spacelabs Ultraview SL (portable monitor)
  - Blood Pressure (BP) via manual cuff or arterial line
    - Spacelabs Ultraview SL2700 or SL

Statistical Considerations

Physiological data (HR, BP, O2, RR) will be recorded throughout the study and analyzed between Groups A and B. Functional and Hospital outcomes will be analyzed to compare group differences at each of the data collection days (0, 5, 10, 15, 20, 30, 45, day of discharge.

Data will be analyzed at the University of Minnesota using the Statistical Package for Social Sciences (SPSS) software program. Test for normality will be completed via a paired t-test for parametric data and via Wilcoxon Rank Sum Test for non-parametric data.

Aim 1: Leg exercise on the Moveo will decrease time to initial ambulation.

- A paired t-test will be used to evaluated time to ambulation in Group A as compared to Group B.

Aim 2: Leg exercise on the Moveo will improve functional outcomes.

- There are 2 primary factors to assess, Group A and B, as well as the impact across time. To assess both factors, repeated measures ANOVA will be used.

Aim 3: Leg exercise on the Moveo will improve hospital outcomes.

- All hospital outcomes, except for discharge disposition, can be assessed between Group A and Group B by a paired t-test.
- Discharge disposition, categorical data, will be analyzed via Chi-Square test.

Data and Safety Monitoring Plan

Study personnel who have completed HIPAA, CITI, and other data management training through the University of Minnesota Medical Center, Fairview and the University of Minnesota will be responsible for the collection, management, and analysis of study data.

Participants will be randomized to groups through a randomization service prior to study initiation. All participants will be assigned a subject number that will be stored on a computer at the University of Minnesota, which is password protected. Data collected from participant's medical records will be managed exclusively by the primary therapist and the PI, and stored in a password protected data management system through Research Electronic Data Capture (REDCap), available at the University of Minnesota.

In accordance with regulations, participant records will be stored for a minimum of three years following completion of the study. After the stated timeframe and if data is no longer needed, records will be destroyed.

Confidentiality

For the duration of the study and data analysis, precautions will be taken to ensure the confidentiality of protected health information (PHI). Such precautions include: the use of password-protected computer for data analysis, PHI storage in the REDCap management program, de-identification of forms and use of assigned subject number, and data collection completed by the primary investigator.

Potential Risks

Lower Extremity Exercise: As with any new exercise program, muscle fatigue or mild soreness may occur in the 24-48 hours following exercise. This minor effect will not impact mobility or function in any way.

Mobilization Protocol: Subjects participating are undergoing ECMO due to respiratory failure and are critically ill. To maximize safety and minimize risks, the primary physical therapist will communicate with the medical team daily to ensure subjects are appropriate for mobilization and participation in physical therapy. Dr. Melissa Brunsvold, Acute Care Surgery physician at the University of Minnesota Medical Center, Fairview, is the primary medical contact for these subjects and is actively involved in the implementation of the ECMO Mobilization Program. Dr. Brunsvold is responsible for removing active physical therapy orders, as is any critical care physician, if an individual undergoing ECMO is no longer stable for mobilization or exercise. Orders will be verified daily, prior to physical therapy, by the primary therapist.

Adverse Event Reporting
Subjects in this study are patients at the University of Minnesota Medical Center, Fairview. As a result, adverse events will be reported not only in the medical record of the subject, but also recorded by the investigator.

Any adverse event will be followed and assessed until it has been determined that the study treatment or participation is not the cause.

Adverse Events

Adverse events observed or reported will be recorded in the case histories of each participant to determine if:

1. The event is directly related to the study and should be classified as a serious adverse event (SAE)
2. A causal relationship exists between the adverse event effect and the investigational exercise/mobility program

Any adverse event not determined to quality, as a SAE will be reported to the IRB with the continuing review progress report.

Stopping Rules

If a SAE occurs, which is deemed by the overseeing physician, Dr. Brunsvold, to be a direct result from the study intervention, the study will be put on hold and reviewed by the PI to determine whether or not the study can continue.

Any deviation from the intended investigational plan to protect the life or well being of a participant in an emergency will be reported to the IRB within 5 working days after the emergency occurred.

As a part of the consent process, participants will be notified that they can withdrawal at any time during the study. Data collected prior to withdrawal of any subject may still be used for data analysis. There is no compensation associated with this pilot investigation.

References

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