

**Prospective Evaluation of Neuromuscular Electrical Stimulation (NMES) for  
Improving Outcomes following Total Knee Arthroplasty (TKA)**

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## **1. PROTOCOL SYNOPSIS**

The present prospective, single-center trial is designed to evaluate the efficacy of CyMedica Orthopedics e-vive™ system, a multifunctional electrotherapy device providing neuromuscular electrical stimulation (NMES), for improving quadriceps strength and accelerating functional recovery in patients managed with total knee arthroplasty (TKA). This post-market clinical trial will involve fellowship-trained Adult Reconstructive orthopaedic surgeons, and include patients who are receiving a unilateral primary TKA. It is hypothesized that the combined preoperative and postoperative use of the CyMedica e-vive NMES can allow for better knee function and allow for a quicker return to function following TKA.

### **1.1 Number Of Sites And Number Of Patients**

The study will be conducted at two sites within the Cleveland Clinic Health System (Main Campus, Lutheran Hospital, and Avon Hospital), and involve a total of 66 patients. All study patients will be divided into three groups: (a) NMES therapy both before and after surgery in addition to standard of care physical therapy (PT); (b) NMES therapy only after surgery in addition to standard of care PT; (c) only standard of care PT.

### **1.2 Study Duration**

Eligible patients will be evaluated according to the time and events schedule (see Table in section 1.4). Clinical outcomes will be assessed from 4 weeks  $\pm$  5 days before day of surgery and followed up after surgery over a 12 weeks  $\pm$  1 week study period.

### **1.3 Outcome Assessments**

These three groups will be analyzed using several outcome measures including validated patient-reported outcome measures the Knee Injury and Osteoarthritis Outcome Score (KOOS) [1], and Veterans RAND 12 item health survey (VR-12)[2], knee active range of motion (extension, flexion), quadriceps femoris muscle (QFM) strength, the Timed Up and Go Test [3] and the Stair Climb Test. The primary endpoint for the study is QFM strength. However, of secondary interest will be: 1) other physical performance measures (i.e. limb symmetry index and gait speed, activity levels), 2) Visual Analogue Scale (VAS) pain levels [4], on outpatient follow-up and immediately before & after NMES therapy, 3) length of stay, 4) Patient dependence on assistive device, 5) Patient satisfaction measures, 6) Patient discharge disposition, 7) Patient readmission rate. The proprietary app for this product will be used to track device usage (intensity, duration of session, frequency of use), knee range of motion and gait speed.

## 1.4 Time and Events Schedule

|                                     | Preop<br>(4 weeks $\pm$ 7 days<br>prior to surgery) | Day of Surgery<br>(- 7 days) | 3 weeks<br>( $\pm$ 7 days) | 6 weeks<br>( $\pm$ 7 days) | 12 weeks<br>( $\pm$ 7days) |
|-------------------------------------|---|------------------------------|----------------------------|----------------------------|----------------------------|
| Outcome Scores                      | X   | X                            | X                          | X                          | X                          |
| Range of Motion                     | X   | X                            | X                          | X                          | X                          |
| QFM strength                        | X   | X                            | X                          | X                          | X                          |
| TUG Test                            | X   | X                            | X                          | X                          | X                          |
| VAS Pain                            | X   | X                            | X                          | X                          | X                          |
| Narcotic usage                      | X   |                              | X                          | X                          | X                          |
| Length of Stay                      |   | X                            |                            |                            |                            |
| Number of outpatient therapy visits |   |                              | X                          | X                          | X                          |
| Patient Satisfaction                |   | X                            |                            |                            | X                          |
| Readmissions                        |   |                              | X                          | X                          | X                          |
| Ambulation assist                   | X   | X                            | X                          | X                          | X                          |

## 2. BACKGROUND

The current standard for rehabilitation after TKA consists of guided exercise therapy for up to 12 weeks after surgery. This includes inpatient, home, and outpatient therapy. The surgery and rehabilitation are highly successful at reducing or eliminating pain experienced preoperatively. However, QFM strength, overall function, and knee range of motion are often worse than preoperative levels for as long as 6 months after surgery and in some cases may persist for many years after that. Such quadriceps strength impairments after TKA have been largely attributed to voluntary activation deficits and can lead to a decrease in functional performance such as decreased gait speed, decreased balance which can lead to falls, and decreased stair climbing & chair rise abilities [5,6]

Since therapy alone does not adequately restore or improve upon the preoperative functional capabilities in a consistent and timely manner, it has been suggested that NMES used adjunctively with postoperative rehabilitation will alleviate the quadriceps muscle activation deficits. Early NMES use after TKA has been shown to: reduce knee extensor lag [7], increase walking speed [8], and improve QFM strength, knee range of motion, and function [5]. However, NMES initiated one month after TKA did not lead to improved QFM strength or function beyond the standard benefits gained from exercise alone [9], thus suggesting that the timing of NMES application after TKA is important.

It has previously been shown that preoperative QFM strength is predictive of postoperative function [10] but the benefit of prehabilitation remains in question [11–13]. To date, there has only been one pilot study assessing the benefits of NMES when initiated preoperatively [14]. This study only included 14 patients (9 NMES, 5 control) but was able to show that preoperative NMES usage may lead to greater QFM strength gains after TKA. Therefore, it will be important to assess the benefits of NMES both preoperatively and postoperatively in order to determine how it will be most beneficial to TKA patients.

### **3. HYPOTHESIS AND SPECIFIC AIMS**

**Study Hypothesis:** Our hypothesis is that use of the CyMedica e-vive™ NMES both preop and postop can improve functional outcomes following TKA.

**Specific Aim 1.** Test whether patients treated with preop and postop NMES show improved physical performance measures when compared to postop only NMES group and standard of care group.

**Specific Aim 2.** Test whether patients treated with preop and postop NMES show improved patient-reported outcomes when compared to postop only NMES group and standard of care group.

**Specific Aim 3.** Test whether patients treated with NMES require fewer outpatient physical therapy visits when compared to the standard of care group.

**Specific Aim 4.** Test whether patients treated with NMES have a decreased discharge disposition to extended care facilities as well as shorter length of stay in extended care facilities compared to standard of care group.

**Specific Aim 5.** Test whether patients treated with NMES have decreased 90 day postoperative readmission rates compared to the standard of care group.

**Specific Aim 6.** Test whether patients treated with NMES have decreased dependence of the use of ambulatory assist devices.

### **4. MATERIALS**

#### **4.1. Control Group**

Control treatment will be standard of care preoperative protocol & standard of care postoperative physical therapy and rehab protocol after TKA. At the end of the study the control group patients will be given the option to cross-over at 12 weeks and receive the NMES device to use.

#### **4.2. Combined Treatment Group**

This treatment group will be given the CyMedica Orthopedics e-vive system 4 weeks ± 7 days before day of scheduled surgery. The patients will begin using the unit until the day before surgery.

Patients will resume using the unit immediately following discharge (POD1 or POD2) + 7 days to take account of a bulky standard of care postoperative dressing, and continuing throughout the first 12 weeks postoperatively. During both preoperative and postoperative phases, patients will be instructed to use the device three times per day while doing activities, 20 minutes each session for 12 weeks.

### *Usage and Compliance*

The use time will be recorded by the device, which is capable of transmitting the information securely to an online application. The usage will be recorded from before surgery, and at the 3, 6, and 12 week visits in order to determine patient compliance with using the device. The acceptable minimum usage to be considered “compliant” with the protocol (for statistical analysis) are as follows:

|                                       | Time Period                            |  |                                     |                                      |
|---------------------------------------|--|--|-------------------------------------|--------------------------------------|
|                                       | <b>4 weeks prior to Day of surgery</b> | <b>Discharge from hospital to 3 week visit</b> | <b>3 week visit to 6 week visit</b> | <b>6 week visit to 12 week visit</b> |
| <b>Usage Recommendation</b>           | 3X per day, 20 min sessions            | 3X per day, 20 min sessions                    | 3X per day, 20 min sessions         | 3X per day, 20 min sessions          |
| <b>Minimum Usage Compliance (80%)</b> | 3X per day, 16 min sessions            | 3X per day, 16 min sessions                    | 3X per day, 16 min sessions         | 3X per day, 16 min sessions          |

### **4.3 Postoperative only Treatment Group**

This treatment group will be given the CyMedica Orthopedics e-vive system only upon discharge after surgery and will be asked to use the device as described in section 4.2.

## **5. ELIGIBILITY**

### **5.1. Inclusion Criteria**

1. Patients undergoing unilateral primary total knee arthroplasty
2. Patients who are between the ages of 18 – 85 years
3. Patient has signed informed consent
4. Patient has access to a smartphone or tablet (Android or iOS)

### **5.2. Exclusion Criteria**

1. BMI  $\geq$  40
2. Inflammatory arthritis
3. Patients who are expected to be in extended care facilities after surgery
4. Patients who have used an at-home NMES device in the past
5. Preoperative daily use of narcotics (i.e., high tolerance)
6. Already enrolled in another research study, including the present study for contralateral knee
7. Other lower-extremity orthopaedic conditions which could interfere with limb function, especially those with significant pain requiring daily analgesic intake
8. Patients with concurrent abdominal, inguinal or femoral hernias
9. Cutaneous lesions in areas of electrode pad placement

10. Patients with a history of epilepsy
11. Patients with a cardiac pacemaker/defibrillator
12. Allergy to adhesives
13. Inability to meet follow-up visits required for the study
14. Patients who are a risk for poor compliance or have a poor understanding of the use of the NMES device
15. Condition deemed by physician or medical staff to be non-conducive to patient's ability to complete the study, or a potential risk to the patient's health and well-being

### **5.3. Subject Identification**

Patients scheduled for a unilateral primary TKA will be identified in EPIC or by ORIS. Those patients that meet the inclusion/exclusion criteria for the study will then be approached about the study in one of the following ways:

1. During a patient's clinical visit. Patients will be given of a copy of the Informed Consent to review.
2. By phone (see phone script). Those interested in participating in the study will be sent a copy of the Informed Consent by mail, and arrangements will be made to complete the consent process and OrthoMidas preoperative data collection during the patient's preoperative clinical visit just prior to surgery.

### **5.4. Randomization**

The patients will not be informed of their treatment assignment until a minimum of 4 weeks  $\pm$  7 days prior to day of surgery. A computer-based randomization generator (SAS, Inc.) will be used to assign patients into treatment arms in a 1:1:1 ratio, using a block randomization method. Patients in the combined treatment group will be given NMES units for device use beginning at at 4 weeks  $\pm$  7 days before surgery. Patients in the postoperative treatment only group will be given NMES units preoperatively and or upon discharge from the hospital. Those patients who are in the postoperative group only who receive the device preoperatively will be instructed to begin using the device only after their surgery. Patients in the control group will not receive any NMES units but will be given the option to crossover and receive a device at the end of the study.

## **6. STUDY PLAN**

### **6.1. Patient Numbering**

Each consecutive patient who presents at the study sites and in whom primary unilateral TKA is planned will be screened for inclusion into this study. Written informed consent must be obtained. Eligible patients will be assigned a unique study I.D. number for confidentiality and data collection purposes. Three-digit numbers will be assigned consecutively to each patient

starting at 001. A master list linking the subject to this unique study ID will be kept by the investigator only in a secure location.

## **6.2. Treatment Plan**

Patients will be randomized to combined treatment group, postoperative NMES only group, or standard-of-care group. From 4 weeks  $\pm$  7 days before day of TKA, the patient will be evaluated until 12 weeks  $\pm$  1 week postoperatively.

### *Preoperative Screening*

Subjects who meet the inclusion criteria and exhibit no pre-operative exclusion criteria will receive a detailed explanation of the study and will be asked whether they are willing to participate in the study. If they agree to participate, written informed consent will be obtained.

The original consent form will be kept with the study records, and a copy of the consent will be given to the subject. A notation will be made in the subject's electronic medical record of participation in the study.

Pre-operative physical findings and a pertinent medical history will then be obtained and recorded on the appropriate case report forms.

Copies of all case report forms completed on subjects will be retained in individual subject files by the investigator in a secure location.

### *Preoperative Care*

At 4 weeks  $\pm$  7 days prior to scheduled date of surgery, a randomization envelope will be opened indicating whether the patient is randomized into the combined treatment group, postoperative NMES only group, or the standard-of-care group. (See section 4 for more detail). Patients randomized to the combined treatment group will begin using the NMES device immediately until the day of surgery. Patients will be thoroughly educated on the use of the device at the time the patient receives the device. Patients may be given the device and educated by either physical therapists and or brace fitting specialists who are participating in the study. In addition, the study sponsor, Cymedica Orthopaedics will be available to provide technical support for the patient at any time if a device malfunction occurs. The study sponsor will not collect any information regarding the patient's status in the study, and will only know that the patient has a device but not which group they are in and or what phase of treatment is occurring. Patients will be asked to use the NMES device at the highest tolerable intensity. At the beginning of the study, all patients will be given an activity monitoring device made by Misfit Wearables®, which is similar to a Fitbit bracelet that they will wear daily. Activity levels will be uploaded and incorporated into online app. We will monitor for any changes in activity/ambulation among the groups to determine the effect of NMES usage on activity.

To ensure the validity of the NMES devices ability to achieve and deliver therapeutic doses in the NMES trial, the NMES device will be set at an intensity that has at least a minimal



therapeutic intensity level that each patient can tolerate. Due to the differences in body habitus as well as anatomic variances of motor nerve branch distributions which may both alter muscle response to electric current, this will be done for each individual patient that will be using the NMES device. Previous studies have determined that the level needed for the NMES device to deliver a therapeutic dose is based on an intensity that will elicit a quadriceps muscle contraction with either visual or palpable superior patellar glide[15–17]. During the patient's preoperative visit at the 4 week mark, each patient will be evaluated using the NMES device by designated trained research personnel who will determine the level of device intensity that is needed to cause superior patella glide, while ensuring the patient is able tolerate the intensity level. The intensity level will then be recorded and monitored through the device application. Patients will be instructed that they need to use the NMES device at least at the level that was determined to be therapeutic, but may increase the intensity as much as they can tolerate. To achieve maximum effective delivery of therapeutic NMES doses in static positions, we will have the patient place their leg that is going to be operated on in a recommended position between 60 to 75 degrees of knee flexion as much as possible while using the device. This will ensure the muscle will be stimulated near its optimal length-tension relationship to maximize the level of evoked force and muscle tension as well as minimizing patient discomfort and muscle fatigue associated with NMES use[15,18,19].

#### *Primary Unilateral TKA Procedure*

At day of surgery (or 7 days prior to scheduled date of surgery), all patients will be evaluated as described previously. (See section 4 for more detail).

#### *Postoperative Care*

Postoperative care will be standardized according to the protocol routinely used at our institution with rapid mobilization, gait training and range of motion [11]. Outpatient physical therapy will be scheduled as needed based on the therapist's assessment of recovery. Physical therapy locations must be Cleveland Clinic affiliated due to the need to use staff who have appropriate training on the NMES device usage to ensure accurate data collection. Pain will be controlled with orally administered long- and short-acting narcotics supplemented by parenteral narcotics as necessary. All study patients will receive standard of care anesthesia protocol.

Following discharge, patients will return for visits with a member of the research team at 3 weeks  $\pm$  7 days, 6 weeks  $\pm$  7 days, 12 weeks  $\pm$  7 days. Data will be collected and reported on the appropriate Case Report Forms at these follow-up visits.

As a last resort, if a patient is unable to keep one of these appointments, he/she will be either be mailed or emailed the OrthoMidas forms so the patient can fill them out. The patient will date and time the forms. They will then send the form back in a pre-addressed envelope. The patients email will be verified by the patient during a clinical visit to ensure accuracy of the correct recipient. Patients not responding to the initial mailer will be contacted by phone and forms may be administered over the phone. The mailers and/or phone calls will allow us to collect all data except the physical function measures. At the completion of the study, patients

will be given a voluntary survey about their experience with the clinical trial, which will be given in person, and or mail and email.

### **6.3 Assessments**

#### **Data collection**

The study duration will be until 12 weeks  $\pm$  1 week postoperatively. Data will be collected (1) 4 weeks preoperatively, (2) prior to hospital admission for TKA, and (3) at 3, 6, and 12 weeks postoperatively (see table in 1.4). All data will be entered and maintained in REDCap, an electronic data capture tools hosted at Cleveland Clinic [20].REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. Only members of the study team (i.e. the personnel listed on the IRB application) will have access to protected health information of patients included in this study.

The following will be collected on all patients in the study and managed using REDCap:

1. MRN
2. Name
3. Date of birth
4. Address
5. Phone number
6. Email address
7. Date of surgery
8. Visit dates
9. Age at the time of surgery
10. Gender: male or female
11. BMI
12. Comorbidities
13. Date of surgery: (month/day/year)
14. Any complications (e.g., emergency department visits, infection, reoperation, etc.)
15. KOOS, VR-12, and VAS pain questionnaire forms

#### **Pretreatment Assessments**

Before treatment, the following assessments/tests will be performed and the results will be recorded on the appropriate pages of the CRF, and or Microsoft excel, Microsoft Word, and REDCap:

- Eligibility criteria, including written informed consent
- Age, gender, height/weight/BMI
- Concomitant diseases
- Physical examination
- Baseline range of motion of affected knee
- Baseline timed up and go test (TUG test, detailed in Appendix A and as described by Podsiadlo et al.)

- Baseline Stair Climb test
- Baseline QFM strength
- Baseline Modified KOOS and VR-12 assessments
- Baseline VAS pain score
- Current medications
- Any use of ambulation assist device

### **Presurgery Assessments**

Before surgery, the following assessments/tests will be performed and the results will be recorded on the appropriate pages of the CRF, and or Microsoft excel, Microsoft Word, and REDCap:

- Device usage patterns (thru app for preop NMES group)
- Range of motion of affected knee
- TUG test
- Stair Climb test
- QFM strength
- Modified KOOS and VR-12 assessments
- VAS pain score
- Current medications
- Activity levels using Misfit Wearables® fitness monitor will be uploaded and incorporated into online app

### **Operative Assessments**

The following will be collected from the Operative and Anesthesia Records and recorded on the appropriate pages of the CRF, and or Microsoft excel, Microsoft Word, and REDCap:

- Surgeon name
- Approach used
- Randomization assignment
- Diagnosis
- Length of surgery
- Estimated blood loss
- Type of anesthesia
- Implant type

### **Postoperative Assessments**

After surgery, one or more of the following will be collected through the online app and at follow-up visits.

- Device usage patterns (thru app)
- Range of motion of affected knee (thru app and at follow-up)
- TUG test
- Stair Climb test
- QFM strength
- Modified KOOS and VR-12 assessments
- VAS pain score

- Length of stay (hospital, extended care facility)
- 90 day readmission rate
- Discharge Disposition (home vs skilled nursing facility vs inpatient rehabilitation)
- Patient Satisfaction measures
- Any use of an ambulation assist aid
- Activity levels using Misfit Wearables® fitness monitor will be uploaded and incorporated into online app

**The NMES device application will not collect any PHI.**

First and last name: will not be included, rather a study ID number. The key will be kept in secure location by research coordinator.

Email: not included

PIN: random number generated

Height, weight, gender: Ok for device app to collect

Date of birth: All study participates will be given a random date of 1/1/2015

Type of surgery: Total Knee arthroplasty Ok for device app to collect

Surgery location: anatomic location, knee

Date of surgery: All study participates will be given a random date of 1/1/2015

**Confidentiality of the data**

All data will be anonymized by assigning study codes. The only document linking study codes to patients will be protected by a password and safely stored on a password protected desktop computer in a locked CCF office. Data obtained will only be shared with individuals who have an active CCF ID and identified as investigators or coordinators in this study protocol. The data will be stored using the intranet database REDCap, Microsoft Excel spreadsheet and Microsoft Word.

**6.4 Withdrawal and Lost to Follow Up**

Patients have the right to withdraw from the study at any time for any reason. The investigator, acting in the best interests of the patient, also has the right to withdraw patients from the study. Any patient requiring in-clinic NMES use more than 4 times during the 12 week follow-up period will be withdrawn from the study. In the event of early withdrawal, efforts will be made to complete and report the observations up to the time of withdrawal as thoroughly as possible. If the reason for removal of a patient from the study is an adverse event, the event will be recorded on the Complications/ Adverse Event Case Report Form. All efforts will be made to follow the patient until the condition resolves or the investigator determines that the patient’s health has returned to an acceptable state.

**6.5 Risks**

On rare occasions, therapy can result in skin reactions such as rash, inflammation, irritation, or electrode burns. The risks associated with the routine aspects of the TKA procedure will be explained to the patient per the surgeon, anesthesiologist and hospital practice.

## **7. CLINICAL OUTCOMES**

### **7.1. Sample Size Justification**

A recent review paper written by Maddocks et al looked at eight different studies that used quadriceps muscle strength as an outcome and created a pooled analysis. They found a standardized mean difference of 0.90 for quadriceps muscle strength between control and NMES intervention groups. Sample size was calculated using this standardized mean difference, along with 80% power and the level of significance (p-value) set to 0.05. This study will require 20 patients per group. However, adding in a 10% expected dropout rate, planned enrollment will be 22 patients per group for a total enrollment of 66 patients.

### **7.2. Statistical Analysis**

Data will be analyzed using intent-to-treat methodology (Herman et al JBJS 2009), utilizing the original treatment group to which a patient was assigned. Differences between means will be analyzed using Student's t-test, while categorical variables will be tested using frequency tabulations comparing outcomes between treatments with the Pearson chi-square test. Differences will be considered significant at the level of  $p \leq 0.05$ .

## **8. PATIENT INCENTIVE PLAN**

In an effort to help bring patients back for all visits and increase device use compliance, patients will be offered \$25 for the 3, 6, and 12 week postoperative visits. In addition, those patients who maintained 80% compliance will be offered a \$200 gift card at the end of the study. The maximum amount a patient may receive is \$275. In addition, parking will be provided for each postoperative visit (\$10/per visit). All patients will be given an activity monitoring device made by Misfit Wearables® at the beginning of the study.

## **9. ADVERSE EVENTS**

### **Adverse Events and Data Monitoring Committee (DMC)**

The Institutional Review Board requires Investigators to monitor and report Adverse Events. The Institutional Review Board is responsible to assess changes in risk to ensure safety protections of human subjects.

### **DEFINITIONS**

An Unanticipated Problem Involving Risks to Participants or Others is any event that (1) is unforeseen, (2) caused harm or placed a person at increased risk of harm, and (3) is related to the research procedures.

**An Adverse Event (AE)** is any untoward or unfavorable medical occurrence, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptoms, or disease. Adverse events can encompass both physical and psychological harms.

**An Internal Adverse Event (AE)** is an untoward medical occurrence, which occurs to participants in research conducted by Cleveland Clinic and/or Cleveland Clinic is the IRB of record.

**External Adverse Event (AE)** is an untoward medical occurrence experienced by subjects enrolled at other institutions for the same study approved at Cleveland Clinic or a different study using the same study drug/device.

**A Serious Adverse Event (SAE)** is any adverse experience that results in any of the following outcomes:

- death
- a life-threatening experience
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant disability/incapacity
- a congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

An Unexpected Adverse Event means any AE not previously known or included in the current Investigator's Brochure, consent form or other risk information.

Related/Possibly Related means there must be reasonable evidence to suggest the event was caused by the drug, device or investigational intervention.

**1. Internal Serious Adverse Events** (events that occur to participants enrolled in research being conducted by Cleveland Clinic or when Cleveland Clinic is the IRB of record) must be promptly reported to the IRB using the IRB AE Report Form within 10 working days from discovery/awareness which meet any of the following criteria as assessed by the PI/Co-I:

- a) Serious, Unexpected and Related/Possibly Related.
- b) AE's determined to be occurring at a significantly higher frequency or severity than expected.
- c) Other Unexpected AE's, regardless of severity, that changes the risk benefit ratio of the study and results in changes to the Research Protocol or Informed

**Consent process/document.**

All Internal SAEs are also reported at continuing review using the AE Summary Log.

**2. External Serious Adverse Events** (events experienced by subjects enrolled at other institutions for the same study approved at Cleveland Clinic or a different study using the same study device/drug) are reportable to the IRB using the IRB AE Report Form within 10 working days from discovery/awareness when:

- a. The External SAE report includes reasonable evidence as assessed by a central monitoring entity [Coordinating or Statistical Center, or a Data Safety Monitoring Board (DSMB) or Data Monitoring

Committee (DMC)] that the event is Serious, Unexpected, and Related/Possibly Related AND places the subjects or others at a greater risk of physical or psychological harm than was previously known or recognized. This will require a change in the protocol and/or consent document.

b. External SAE reports provided by the Sponsor to the investigator indicating the event is Serious, Unexpected and Related/Possibly related but without reasonable evidence or DSMB/DMC determination of greater risk are not reportable to the IRB within the 10 day window. Without Sponsor evidence or assessment the implications of the event cannot be determined by the research team and therefore need not be reviewed. These SAE' shall be placed on the AE Summary log to be submitted at the annual continuing renewal.

3. **DEATHS** are to be reported to the IRB using the IRB AE Report Form according to the following guidelines:

a) Internal Death

- Related/possibly related whether expected or unexpected– within 5 working days from discovery/awareness
- not related and expected – at time of continuing review
- Not related and unexpected – at time of continuing review except cancer studies Cancer: Not related and unexpected within 10 working days from discovery/awareness

b) External Death

Related/possibly related and unexpected – within 5 working days from discovery/awareness not related whether expected or unexpected – at time of continuing review related/possibly related and expected – at time of continuing review

c) ALL Deaths are also reported at time of continuing review using the AE summary log.

4. **Non-serious Adverse events** (Internal and External) that are both Related/Possibly related and unexpected are reported on the AE Summary Log at time of continuing review to assess trends.

5. An IRB staff (a qualified, licensed practitioner assigned to this function by the IRB chair and IRB Executive Director) reviews Adverse Event Reports to determine whether they represent Unanticipated Problem Involving Risks to Participants or Others. Events that are assessed, by either the IRB Staff or Investigator, to place subjects or others at a greater risk of harm than was previously known or recognized, or changes the risk/benefit ratio of the study, or requires a change in the protocol and/or consent document are referred to Full Board for review under Policy #70.

Events that do not involve risk to Participants or Others or changes to the informed consent or protocol do not require further review. Investigators are informed of the determination and the IRB file is updated.

6. The AE Summary Log is reviewed by the IRB at the time of continuing review to identify trends in frequency and severity which may impact subject safety.

This study is an Investigator Initiated research trial. Each study site will be considered its own regulatory sponsor and is responsible for internal data monitoring and any study reporting required by ClinicalTrials.gov.



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## **Appendix A**

### Timed up and go test (TUG test)

#### Set up

1. Wrist watch with second hand or stop watch to time performance
2. Standard arm chair (approximate seat height of 46 cm, straight back)
3. Line on floor 3 meters from chair

#### Procedure

1. Subject wears his regular footwear and uses his customary walking aid.
2. No physical assistance is provided.
3. Subject starts with his back against the chair, his arms resting on the chair's arms, and his walking aid at hand.
4. Instruct subject that, on the word 'go', to get up and walk at a comfortable and safe pace to the line on the floor, turn, return to the chair, and sit down again.
5. Allow subject to practice the test once before being timed to become familiar with the test.

\* Podsiadlo D, Richardson S. The timed 'Up & Go': a test of basic functional mobility for frail elderly persons. *J Am Geriatr Soc* 1991;39:142–8.