- ## Protocol Information

Title: Development of a Neural Interface for Powered Lower Limb Prostheses
Proposal No: 07211001

- ## Sponsor Information

This study is being sponsored by the Department of Defense (DOD) Telemedicine and Advanced Technology Research Center (TATRC).

- ## Principle Investigator

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- ## Institutions Engaged in Research

Rehabilitation Institute of Chicago / Northwestern University

Assurance No: FN00001549
Assurance Expiration Date: 6/30/2014
IRB of Record for This Study: Northwestern University IRB
Key Person: Todd Kuiken, MD, PhD

Description of Study Activities
The Rehabilitation Institute of Chicago, an Academic Affiliate of Northwestern University, will be responsible for subject recruitment, data collection, and data analysis. The amputee sockets will be constructed in an on-site prosthetics laboratory and attached to the prostheses by a certified prosthetist. Data will be collected in a gait lab with appropriate ambulation aides, safety mechanisms and EMG signal capture capabilities.

- ## Study Information

Type of Research: Biomedical Research

- **Study Design**

Background and Significance

Major lower limb (above ankle) amputation is a significant impairment in over 650,000 people in the U.S., where 78% of these amputations were due to vascular disease in the elderly population (Ziegler-Graham et al., 2008). This population will potentially benefit most from powered devices, as many are unable to ambulate well on passive devices and opt for a wheelchair instead, especially transfemoral amputees (Davies and Datta, 2003). Most prosthetic limbs for transfemoral amputees are mechanically passive and behave like springs and dampers. Although many transfemoral amputees can walk on level surfaces with a passive device, they do so asymmetrically in an energetically unfavorable manner, expending up to 60% more metabolic energy than healthy subjects (Waters et al., 1976). Additionally, lower limb amputees with these devices tend to have great difficulty navigating more demanding terrain such as ramps and stairs (Schmalz et al., 2007). More advanced lower limb prostheses have recently been developed with an onboard electronic system (Otto Bock Orthopedic Industry, 1998) which allows for variable knee damping. These devices help improve functional outcomes in clinical tests, such as allowing for better loading responses and decreased metabolic cost (Johansson et al., 2005). To do more strenuous tasks such as step-over-step stair ascent (Figure 1) and to aid less physically fit amputees that have difficulties on passive devices, powered lower limb prostheses are being investigated. Powered prostheses may also help with many of the problems that transfemoral amputees face, (Au et al., 2009) such as decreased balance (Miller et al., 2001a), slower self-selected walking speeds (Boonstra et al., 1993), larger metabolic energy expenditure (Waters et al., 1976) and greater predilection to falling (Miller et al., 2001b) as compared to healthy individuals.

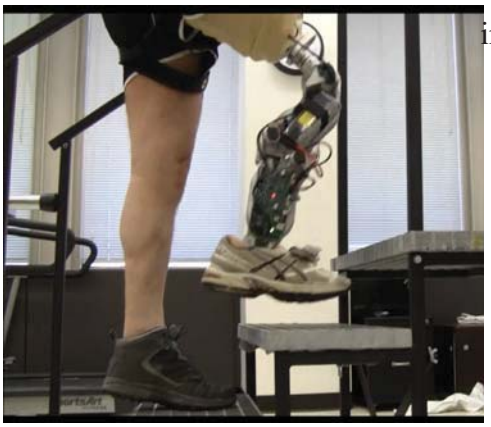

Figure 1: Vanderbilt's powered prosthetic knee/ankle device during stair ascent.

Figure 2: Example of EMG electrode placement on the residual limb of a transfemoral

Powered prostheses have the ability to produce positive mechanical power at the knee and ankle (Highsmith et al., 2010) (Hitt et al., 2010). These devices are typically instrumented with a number of sensors to detect gait phase transitions to appropriately modify the impedances rendered at of the knee and ankle. (Fite et al., 2007). Impedance based control (output torque as a function of angular displacement) for these devices has been proposed to allow the user to interact naturally with their environment, as compared to the simpler position based control which enforces

a fixed trajectory (Au et al., 2008). Finite state machines are used to change between the desired impedance properties of powered leg prostheses for different gait phases and activity modes. A missing component from these controllers is to achieve seamless transitions between these states, as current controllers often require unintuitive user input to change activity modes. Thus an intent recognition system that can predict the intended activity mode before the prosthesis needs to transition to any given activity is necessary.

Two broad sets of sensors have been previously considered for intent recognition: mechanical sensors in the prosthesis itself and EMG sensors in the amputee's socket on the residual muscles (Figure 2) (Huang et al., 2009). The mechanical set includes sensors such as IMUs (inertial measurement units), potentiometers and encoders. These types of sensors can only respond to the movements of the prosthesis and the user. The second set is EMG sensors, which provide information that can precede rather than react to the user's intended movements. Information that precedes movement onset would be highly valuable for early identification of planned activity mode transitions.

For upper limb prostheses, EMG-based control from residual limb muscles has been used clinically for decades (Sears and Shaperman, 1991), and pattern recognition based EMG control is nearing clinical implementation (Lock et al., 2011). For these strategies, the amputee is trained to perform steady muscle contractions to move the prosthesis. Thus, the features of the EMG are assumed to remain stationary in a time window. In the lower limb, this type of control has not been available as most prosthetic legs are not powered. With the heightened ability to modify the gait characteristics of an amputee using a powered device (Sup et al., 2008b), a neural based control may be beneficial for enabling more advanced functionality and controllability of the device, by predicting user intent (Huang et al., 2009) (Ha et al., 2011). However, lower limb EMG patterns change throughout the gait cycle (Winter, 1983), invalidating the stationary assumption. Therefore, a gait classification strategy should utilize the patterns of EMG activations over the gait cycle to help determine user intent. Such an approach has not yet been developed.

Bayesian techniques are a powerful strategy to incorporate information over time and have been shown to perform comparably to other techniques for discriminating EMG patterns using pattern recognition (Hargrove et al., 2007). A method that predicts discrete classes (*e.g.* activity mode) using continuous observations (*e.g.* sensor features) is a Hidden Markov Model. These types of dynamic Bayesian networks incorporate past information with current sensor information in a probabilistic approach (Rabiner, 1989). One example demonstrating the usefulness of incorporating past information is that certain transitions are much more likely than others, for example a walking to stair ascent transition is much more likely than a stair descent to ramp ascent transition. Hidden Markov Models assume stationary signals over time; thus a modified DBN that relaxes this assumption will be used. Time history information is needed for lower limb classification to utilize patterns of EMG throughout the gait cycle by continuously monitoring the EMG activity and incorporating the information through each time step of the model.

Multiple intent recognition strategies have been proposed to perform transitions between activity modes for lower limb prostheses. One of the first methods published is called "echo control" (Flowers and Mann, 1977) in which the prosthetic leg mimics the sound limb. This approach has the disadvantages that the user must have an even number of steps, always lead with the sound limb, and be a unilateral amputee. Also the sound side must be instrumented and performed tasks must be symmetric. More recent studies have begun to look at using pattern recognition to predict prosthesis activity mode. In Huang et al. (2011), the researchers demonstrated accuracy above 95% for recognizing activity modes offline with amputees walking on an instrumented passive prosthesis. In Varol et al. (2010), one transfemoral amputee performed sitting, standing and level walking using a powered prosthesis and achieved high recognition rates. These studies demonstrate the great potential of using pattern recognition for lower limb prosthesis control.

Research Objectives

This work is innovative in the lower limb prosthesis control field in the following three ways: 1) **no known studies have done real-time intent recognition traversing different types of terrains such as stairs and ramps.** 2) None of the intent recognition strategies proposed so far incorporate time history information to predict activity mode. 3) Finally, this will be the first study to record EMG with a powered lower limb prosthesis and use it in real-time for intent recognition purposes during locomotion.

Given the above considerations, our primary objective is to determine the extent to which EMG signals and time-history information improve the real-time control (ie intent recognition) of a powered knee-ankle prosthesis during a set of locomotion activities. Secondary objectives are to examine data offline to determine the contribution of EMG and time-history information individually, and to correlate online/offline performance metrics (ie classification error/accuracy). The *working hypothesis* is that the utilization of time history information and current sensor information incorporated in a DBN with EMG information will increase the prediction accuracy compared to only using current mechanical sensor information.

Protocol

This research will use an AB/BA cross-over design. Real-time intent recognition systems will be tested. The order of testing will be randomized and the subjects will be blinded to the testing condition. Based on a power analysis from related work (Huang et al., 2011), 7 transfemoral amputees will be required. For more information, see the Statistical Analysis Plan Below.

A lower limb prosthesis with powered knee and ankle actuators was provided by Vanderbilt University; its design has been reported in detail previously (Sup et al., 2008b). This prosthesis contains onboard electronics and sensors and is controlled by specifying impedance parameters—stiffness, damping, and an equilibrium angle – for both the knee and ankle. This is done through custom software developed by the Center for Bionic Medicine called CAPS (Control Algorithms for Prosthetic Systems). This software implements a finite state machine to switch between impedance parameters for the prosthesis. Each activity mode has multiple impedance states to appropriately actuate

the prosthesis for different phases during the gait cycle. For example, the level walking activity mode has separate impedance parameters for early/mid stance, push-off, swing flexion, and swing extension. One current limitation of the system is that the activity mode can only be changed at heel contact or toe off (twice per stride) for safety concerns.

For each subject, the powered prosthesis will be fit to the patient by a certified prosthetist. Impedance parameters of the leg will be adjusted until the subject demonstrates satisfactory locomotion capabilities for all activity modes as determined by a skilled physical therapist.

Data Collection

Subjects will walk using the powered prosthesis through a specific circuit that will include standing, walking, ramps, stairs, and turning activity modes. For these trials, EMG will be collected within the socket attached to the residual limb of the amputee using a custom 16 channel EMG system. Electrodes will be placed on at least 4 residual limb muscle locations including at least one muscle from: 1) hip extensor group, 2) hip flexor group, 3) hip abductor group, 4) hip adductor group. During the experiment, signals a total of at least 17 sensors will be recorded simultaneously for the purpose of intent recognition. The sensors consist of potentiometers and encoders for both knee and ankle to give position and velocity information, a six degree of freedom inertial measurement unit (IMU) located on the shank (the IMU includes three accelerometers and three gyroscopes), a single axis load cell oriented longitudinally with the shank, and the EMG sensors. Raw data will be sampled at 1 kHz with a 16 bit A/D resolution and sent through a tether from the prosthesis to a desktop computer for storage.

For the first set of data (consisting of 10-20 repetitions of the circuit described above), the experimenter will manually trigger gait transitions between activity modes to achieve seamless transitions during data collection. The recorded data and a set of corresponding labels of the activity mode for each data point will be used to train an intent recognition system specific to the patterns generated by each individual amputee. Once the intent recognition system is trained, two additional sets of circuits (10-20 repetitions each) will be performed by the amputee using the real-time intent recognition: one set with time history classification and EMG + mechanical signals and one with instantaneous classification and only mechanical sensors. The order of testing the real-time control system will be randomized and the subject and clinicians assisting with the experiments will be blinded to the real-time control system under investigation. In all real-time control conditions, both the intended activity mode and the actual activity mode chosen by the intent recognition system will be recorded to determine the real-time accuracy of the system.

Signal Processing and Classification Approach

Data will be separated by both their phase label (swing or stance) and the upcoming activity mode. Thus data directly before a transition will be associated with its future activity mode to enable an intent recognition system able to learn to predict future transitions.

Typical pattern recognition steps include preprocessing the signals (filtering), data windowing, feature extraction, and classification (Oskoei and Hu, 2007) (Figure 4). EMG will be filtered using a band-pass filter with cutoffs of 20 and 420 Hz. Next, data will be windowed in groups of 100-500ms before a significant event in the gait cycle. The analysis window size will be chosen to maximize classification performance. Feature extraction for the mechanical sensors will consist of simple features: mean, standard deviation, minimum, and maximum (Varol et al., 2009). For the EMG signals, features typically calculated for upper limb myoelectric pattern recognition will be used, including mean absolute value, number of zero crossings, number of slope sign changes, waveform length and autoregressive features (Englehart and Hudgins, 2003; Huang et al., 2004; Hudgins et al., 1993). For classification, a time history strategy will be compared to an instantaneous strategy.

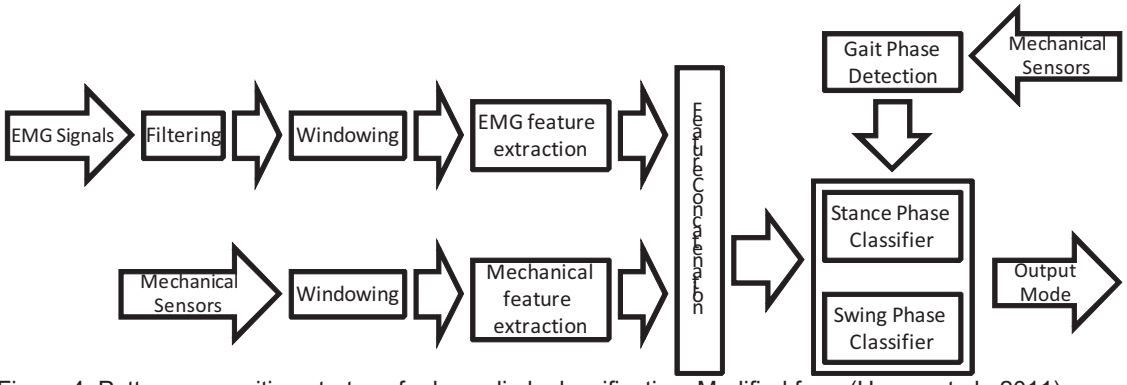

Figure 4: Pattern recognition strategy for lower limb classification. Modified from (Huang et al., 2011).

Error rates will be generated based on what actually happened (what the intent recognition system chose) compared to the intended activity mode. From this, multiple comparison metrics will be used including the overall classification error, the error at transition steps, within-mode error, and the spurious misclassification rate (metrics described in preliminary studies section). Additionally, a confusion matrix detailing all the errors between all the activity modes will be used to evaluate strategies. A paired t-test will be used to compare classification error between the two classifier models (time history with EMG and instantaneous). Offline error will also be computed to understand the contribution of the time history information compared to the EMG information. For this offline analysis, similar error rates will be obtained for four conditions: 1) EMG + mechanical sensors with time history classification, 2) mechanical

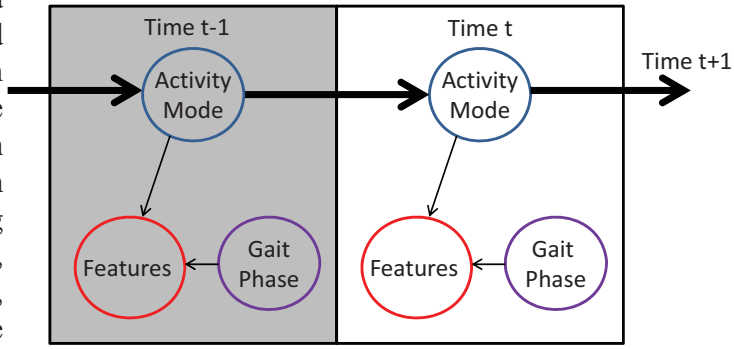

Figure 5: Dynamic Bayesian Network intent recognition strategy. At each time point, activity mode is determined based on known features and gait phase as well as priors propagated based on the probabilities at the previous time slice (dotted lines).

sensors with time history classification, 3) EMG + mechanical sensors with instantaneous classification, and 4) mechanical sensors with instantaneous classification.

Instantaneous classification for this study will be implemented using the maximum likelihood approach which is a common approach in pattern recognition prosthesis control literature. This method computes the probability that data were generated under each of the classes (activity modes). Thus, at each time step, a probability that the data was generated by walking, standing, ramp ascent, ramp descent, stair ascent, and stair descent is calculated. The activity mode with the highest probability—the maximum likelihood estimate (MLE) or $\hat{C}_{MLE}$– is selected as described by equation 1, where $\vec{x}$ is the feature vector and C is the activity mode (or class).

$$\hat{C}_{MLE} = \arg\max(p(\vec{x}|C)) \quad (1)$$

Time history information will be implemented using a Dynamic Bayesian Network due to its computational efficiency, which is critical for this study because of real-time requirements. The computational efficiency of the DBN is due to the Markov assumption, which states that future decisions are conditionally independent of past states given the present state. The DBN uses Bayes law to calculate the maximum a posteriori (MAP) estimate (equation 2), which is the class with the maximum posterior probability $p(C|\vec{x})$). The MAP estimate is a combination of past information in the form of a prior and current information (the likelihood). The prior ($p(C)$) is the probability based on past information of being in any of the classes. Thus the MAP estimate is calculated from equation 2 where $p(\vec{x}|C)$ is the likelihood probability, $p(\vec{x})$ is the observational probability, and $\hat{C}_{MAP}$ is the MAP estimate.

$$\hat{C}_{MAP} = \arg\max(p(C|\vec{x})) = \arg\max(\frac{p(\vec{x}|C)p(C)}{p(\vec{x})}) \quad (2)$$

The priors for each step are calculated based on equation 3, which is a matrix multiplication of the previous step's posterior probabilities ($p(C|x)_{t-1}$) and a transitional probability matrix (Φ). The transitional probability matrix (Φ) is learned from the data and describes the probability of transition between any two activity modes.

$$p(C)_t = p(C|x)_{t-1} * \Phi \quad (3)$$

Because signals are not stationary during the gait cycle, a separate likelihood model was formed for stance and swing phases of the gait cycle. The form of the DBN implemented for intent recognition is displayed in Figure 5. Activity mode is determined at each time step by Bayesian inference in which the features at each time step are known, as are the gait phases based on the load cell. This model will be used to calculate activity mode based on time history information.

Statistical Analysis Plan

The experiment was powered to detect significant differences between the 2 real-time control conditions previously described. The sample size was computed by performing a power analysis from data published by Huang et al (Huang, 2011). Type 1 error (α) was

set to 0.05 and type 2 error (β) was set to 0.20. Data will be tested for normalcy and a two-sided paired t-test will be used to check for significant differences. The clinically meaningful difference was set at 5% classification error. A post-hoc test will be used to determine the effect that time-history and EMG information has individually using the offline date. This will be done through a 1-way ANOVA analysis to compare the error rates of the four offline conditions (see Signal Processing and Classification Approach section). Finally, the online performance will be correlated with the offline accuracy to investigate the relationship between the two variable*s*

- **Inclusion/Exclusion Criteria**

Amputees and able-bodied subjects will be recruited with IRB approval, informed consent, and without bias of race or gender. Able-bodied subjects will be attached to the prosthesis using bypass sockets and will be used primarily in the development phase of creating the.

Inclusion – Amputee Subjects

- Lower limb amputees
- K3/K4 ambulators
- age constrained from 18 to 80 years old

Exclusion – Amputee Subjects

- over 250 lbs body weight
- inactive, physically unfit
- cognitive deficits or visual impairment that would impair their ability to give informed consent or to follow simple instructions during the experiments
- Pregnant women
- co-morbidity that interferes with the study (e.g. stroke, pace maker placement, severe ischemia cardiac disease, etc.)

Inclusion – Able-bodied Subjects

- no injury on either lower extremity
- age constrained from 18 to 80 years old

Exclusion – Able-bodied Subjects

- inactive, physically unfit
- over 250 lbs body weight
- cognitive deficits or visual impairment that would impair their ability to give informed consent or impair their ability to follow simple instructions during the experiments
- Pregnant women (status determined by self-reporting)
- co-morbidity that interferes with the study (e.g. stroke, pace maker placement, severe ischemia cardiac disease, etc.)

- **Subject Recruitment and Screening**

  Lower limb amputees will be recruited primarily from the amputee clinics at the RIC; however, subjects who responded to a similar research protocol, IRB STU00000373, will also be considered. The clinicians in the RIC amputee clinic (Walter Afable, CP, Nicole Soltys, CP, George Du, CP, Kelly Lee, CP, Sarra McClintock, CP), and at Northwestern University Prosthetics-Orthotics center (Robert Lipschutz, CP) will be informed that CBM is looking for lower limb amputees who, in their judgment, are good ambulators. Specifically, they will be told that amputees should be capable of level ground walking and capable of ascending and descending stairs with or without the use of hand rails. Potential research subjects will be referred by the clinicians to Robert Lipschutz, CP, Elizabeth Halsne CP or Laura Miller CP, both who are affiliated with the Center for Bionic Medicine. They will watch the patient walk using their normal prosthesis to confirm that they are good ambulators and examine the patient's residual limb(s) to determine if there are any limitations to EMG signal measurement, such as excessive scar tissue. Finally, Dr. Todd Kuiken, MD, PhD will screen the potential patients to ensure that that they meet the inclusion/exclusion criteria. Dr. Kuiken may also recruit previous patients that he has treated.

  Able-bodied control subjects will be recruited from the staff and students at the Rehabilitation Institute of Chicago and Northwestern University. This will be done primarily through word of mouth. Potential subjects will be directed to Levi Hargrove, PhD. Potential subjects will be informed of the time commitment required and questioned with regards to the inclusion/exclusion criteria.

- **Informed Consent Process**

  Informed consent to participate in the study will be obtained per IRB protocol. We will explain the study verbally including time commitments, compensation, and potential risks and collect no written data. The subjects will be asked if they still wish to participate and will be given an informed consent form. Subjects will read the informed consent sheet and initial the bottom of each page. A researcher will assign a confidential subject code to the participant and be available to answer any questions which arise from the informed consent sheet and witness the consent process. Subjects will be informed that participation is strictly voluntary and they can withdraw from any experiment at any time for any reason without consequence. Women of child bearing age will be informed that they should not participate in this study if they are pregnant, due to the potential of falling. Potential female participants will be questioned with regard to their pregnancy status to determine if they meet the inclusion criteria. They will also be asked to notify the study doctor if they become pregnant, at which point they will be withdrawn from the study.

- **Labeling and Storage of Collected Data**

All recorded data will be stored on a secure computer at CBM for further offline analysis. Hard copies of collected data and motion capture will be stored in a locked cabinet at CBM. Each subject will be identified with a subject code, and filenames will be labeled with the subject code instead of subject name. In the case that the results of this data are published, the subjects will be referenced through the subject code and the identity of the research subjects will not be indicated. The data will be destroyed when it is deemed no longer scientifically relevant. Accurate and complete study records will be maintained and made available to representatives of the U.S. Army Medical Research and Materiel Command. These representatives are authorized to review research records as part of their responsibility to protect human research volunteers.

- ## Risk and Injury

The primary risk in this protocol would be injury due to falls, regardless of the prosthesis being used. Fall prevention is of paramount importance, and the risk has been abated as listed above, through use of harnesses, researcher assistance with gait belts, handrails, walkers, and other clinically appropriate ambulation aides. Furthermore, all subjects will begin with simple activities such as level-ground walking and will only be asked to complete more difficult activities after they become proficient users. Other risks include skin irritation and muscle strain. Skin can become irritated while using any prosthesis and it may also become irritated by adhesive electrodes. To abate the risk of skin irritation, a properly fitting socket(s) will be constructed by a certified prosthetist and the residual limb(s) will be checked periodically for skin irritation. To reduce the irritation associated with adhesive electrodes, the limb will be wiped with alcohol to remove adhesive and electrode gel residue. Muscle strain is a common problem with abnormal gait or when walking with a new prosthesis. To prevent this, experimental sessions will be kept as short as possible, adequate rest periods will be provided between trials, and the subjects will be questioned with regards to discomfort. Metabolic measurements are often measured from pathological populations including amputee subjects. The risk to the patient of taking such measurements is very low.

The instrumented passive prosthesis was constructed by a certified prosthetist and has been successfully used during a number of activities to simultaneously collect physical sensor and surface EMG data as per IRB STU-0000373. The powered transfemoral prosthesis equipped with a control system relying on prosthesis sensor data was constructed by collaborators at Vanderbilt University and has been tested on amputees and able bodied subjects for a number of activities at Vanderbilt University and Walter Reed Medical Center.

- ## Benefits

The primary benefit in this research is the development of a superior lower limb prosthesis and associated control. We believe this is cutting edge research that will

open up a new branch of translational science and demonstrate exciting new potential to improve lower limb ambulation in amputees including: enabling the subjects to walk on a great variety of terrains with markedly improved human efficiency. We hope that this will lead to a commercially viable, neural, lower limb control system. Valuable scientific data will be recorded and published. There is no immediate benefit to the subjects; however, the long-term benefit to the population of lower limb amputees could be substantial.

- **Compensation**

Compensation for local amputee patients will be $40.00 per hour rounded up to the nearest hour. The participation of non-staff able-bodied subjects will be compensated at a rate of $20.00 per hour (rounded up to the nearest hour). If there are any amputee participants from outside the Chicagoland area, they will receive a stipend of $250.00 per day, up to 3 days or completion of all experimental components plus the cost of lodging, travel, and parking if necessary. Such arrangements will be facilitated by RIC staff. These compensation rates are consistent with other approved IRBs. In the event that subjects become unable to complete all components of the experiment, they will receive compensation for their involvement up to the point where they were unable to continue. For hourly subjects this would mean that they would receive a stipend rounded to the nearest hour when participation ended. In the event that out of town subjects decide to not complete all components of experiment they will be paid for all the days they did participate, whether completing each task or not. Stipends will not be prorated. Meals are not included in compensation; however travel (bus, taxi, train) will be covered. Payments in excess of $600 in a calendar year are required to be reported in taxes as income. There are no initial plans to involve active duty personnel. Retire service members will hopefully be recruited to participate as civilian subjects. All stipends will be mailed to eligible participants within 30 days.

- **Confidentiality**

All data and medical information collected from subjects will be considered privileged and held in confidence. Subjects will be identified by a subject code number in any presentation of the results. The subject code list, data, and videotapes will be stored on a secure computer at RIC. Hard copies of the data will be stored in a locked cabinet and destroyed when it is deemed no longer scientifically relevant. Complete confidentiality cannot be promised to subjects, particularly to subjects who are military personnel, because information bearing on their health may be required to be reported to appropriate medical or command authorities.

- **Adverse Events**

All unanticipated problems involving risk to subjects or others, serious adverse events related to participation in the study and subject deaths related to participation in the study will be promptly reported by phone (301-619-2165), by email

(hsrrb@det.amedd.army.mil), or by facsimile (301-619-7803) to the USAMRMC, Office of Research Protections, Human Research Protection Office. A complete written report will follow the initial notification. In addition to the methods above, the complete report will be sent to the U.S. Army Medical Research and Materiel Command, ATTN: MCMR-ZB-PH, 504 Scott Street, Fort Detrick, Maryland 21702-5012.

- ## Changes to Protocol

Any deviation to the protocol that may have an effect on the safety or rights of the subject or the integrity of the study will be reported to the ORP HRPO as soon as the deviation is identified.

Cited Literature

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