Wireless Prosthetic Control Effectiveness Study

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Protocol: Wireless Non-Invasive Advanced Control of Microprocessor Prostheses and Orthoses II

Note 1: Figure and citation *numbers* refer to those in the original grant application that funds this work. Referenced figures are shown herein but are not numbered starting from "1" and numbering does not advance sequentially. Any new figures (that did not appear in the original grant application) are referenced by letter (i.e., "A", …).

Note 2: We believe that our use of this prototype re-chargeable, wearable electrode is *exempt* from requirement of an Investigational Device Exemption (IDE) prior to initiation of the experimental work because its use does *not involve significant risk* (https://www.fda.gov/medical-devices/investigational-device-exemption-ide/ide-application). The wireless electrode is non-invasive. It does not by design or intention introduce energy into a subject. It monitors muscle electrical activity (electromyogram, or EMG) non-invasively. The device is battery powered and the battery is only charged when the device is not in operation on the subject (i.e., the battery is charged while sitting on a desktop). (See Figure A below for a mock-up view of the wireless electrode.)

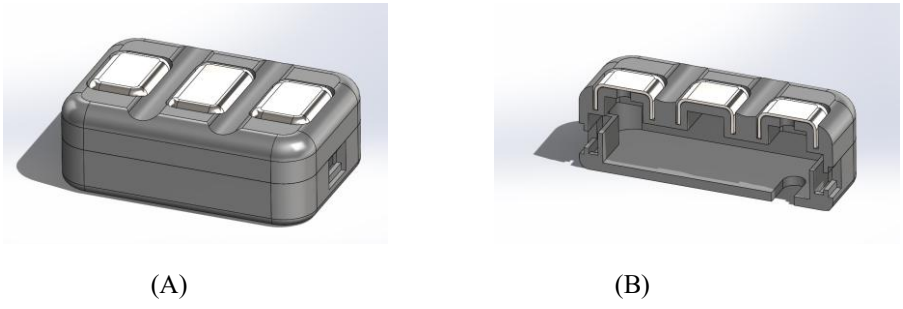
HUMAN SUBJECT TESTING LABORATORY AND TAKE-HOME STUDY

Figure 5 | Photograph of prosthetic liner

There are multiple advantages to wearing a prosthetic liner (i.e., a sleeve most commonly made from silicone or thermoplastic elastomer material and covered in fabric) [Figure 5] that have made them very popular with lower limb prosthesis wearers. These advantages include improved comfort, improved suspension, and potentially less aggressive socket trimlines. However, upper limb prosthesis users with myoelectric control cannot wear a liner as the electromyogram (EMG) electrode must touch the skin to transduce the myoelectric signal. Therefore, upper limb users miss out on the comfort and suspension benefits of the liner, while also not being able to use prosthetic socks for limb volume management. Therefore, upper limb myoelectric users would benefit from the ability to wear prosthetic liners.

The proposed ASTERISK system would allow for liners to be worn with upper limb myoelectric systems. By creating wireless sensors that can be worn under a liner, the sensors can be placed on the skin to collect the myoelectric signal, the liner then rolled over the top of the sensors when donning, and the sensors can transmit the EMG signal wirelessly to the prosthesis.

Our overall hypothesis is that allowing users to wear a liner with their myoelectrically-controlled prosthesis will allow them to realize the benefits of liners and therefore increase their overall satisfaction with the prosthetic device while not sacrificing functional performance. Stated more explicitly, our primary hypothesis is that myoelectric prosthesis users will show an improvement in device satisfaction, as measured by the Orthotics and Prosthetics User Survey (OPUS)—Satisfaction with Device (SD) survey, when using a prosthetic liner with our "ASTERISK" wireless EMG electrodes (Figure A) as compared to their standard myoelectric prosthesis. The OPUS-SD was selected because it is a self-report measure that focuses on prosthesis fit, comfort, skin health, etc., is likely to be sensitive to the proposed intervention, and has established validity and reliability in prosthesis users [15,16]. Figure B shows a diagram of a complete hand prosthesis using our wireless electrode system. As shown, two separate electrode nodes are independently secured to the forearm, one over flexion muscles and the other over



(A) (B)

Figure A | Front view (A) and cut-away cross-section view (B) of a mock-up of our proposed wireless, re-chargeable electrode. Overall dimensions are 30 mm length x 20 mm width x 10 mm height. Both views show the two recording electrode contacts with a reference electrode contact between them. The electrode contacts are held in electrical contact with the skin over the muscle(s) of interest during use.

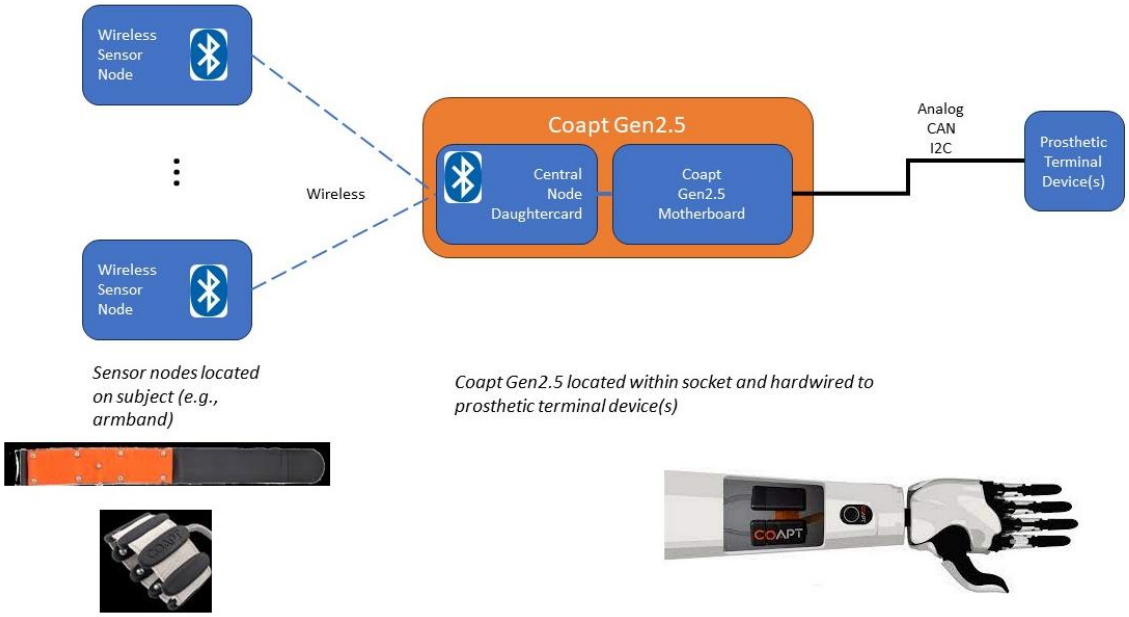


Figure B | Top shows a diagram of our hand prosthesis system. Each "Wireless Sensor Node" is a battery-powered electromyogram (EMG) electrode-amplifier in its own separate, independent case. [Figure A (above) shows how such electrode nodes might look.] One electrode node would typically be applied over remnant *flexion* muscles in the forearm and the other over remnant *extension* muscles in the forearm. The electrode nodes are held in place by an armband. These nodes transmit wirelessly to a receiver-controller that is integrated into the hand prosthesis near its wrist (labelled "Coapt Gen 2.5" in the diagram). The receiver-controller receives the EMG signals and generates hand control commands that are issued (via electrical wires) to the adjacent hand. The photo in the lower right, shows a Coapt Gen 2.5 integrated into the wrist section of a hand prosthesis.

extension muscles. The receiver is then integrated into the hand prosthesis. The received electromyogram signals are used to control the prosthetic hand, which is electrically wired to the receiver-controller.

In addition to our primary hypothesis, we will also evaluate multiple secondary hypotheses such as the reported Socket Comfort Score (SCS), all or portions of the Prosthesis Evaluation Questionnaire (PEQ), elbow range of motion (due to the ability to use less aggressive socket trimlines), and wear time of the prosthesis (i.e., greater comfort/satisfaction should lead to longer wear). The Socket Comfort Score was developed to assess socket fit and has evidence of validity and sensitivity to changes in socket fit [17]. We plan to utilize the recently released expanded SCS version, that has shown superior psychometric performance to the original [18]. The Prosthesis Evaluation Questionnaire is comprised of nine scales, each of which can be administered independently. These scales measure ambulation, appearance, frustration, perceived response, residual limb health, social burden, sounds, utility, and well being. To monitor upper limb prosthesis usage, we will deploy the methods used in prior studies to monitor linear acceleration, rotation and orientation (with respect to gravity) of the prosthetic limb [19] (e.g., ActiGraph GT9X activity monitors).

Finally, to demonstrate that the improved comfort does not come at the expense of decreased function, we will also collect functional outcomes measures in the laboratory, including the Activities Measure for Upper Limb Amputees (AMULA) [20]. A secondary hypothesis is that we will demonstrate equivalency between the two test conditions (i.e., standard socket configuration vs. liner with ASTERISK wireless electrodes socket configuration). The AMULA is attractive because it 1) evaluates the use of the prosthesis in a relatively large distribution of "zones" (i.e., over the head, below the waist, etc.) that have the potential to create control challenges due to electrode liftoff, 2) requires the use of a large percentage of bi-manual tasks (to ensure that tasks cannot simply be completed with the unaffected limb), and 3) has had its psychometric attributes established on our proposed study population (to ensure its reliability and validity) [21].

STUDY DESIGN

The study evaluates the ASTERISK system to determine if ASTERISK will increase a user's self-reported satisfaction with their prosthesis as measured by the Orthotic and Prosthetic User Survey—Satisfaction with Device (OPUS-SD) when compared to their current prosthesis. While the technology has the potential to benefit other patient populations, we will focus this initial pilot study on individuals with trans-radial limb absence to reduce potential confounding variables associated with including other amputation levels.

We plan to conduct a randomized 2x2 crossover study to evaluate benefits provided by prostheses utilizing liners with the ASTERISK electrodes over standard prostheses. The study design is shown in Figure 25 with the two crossover test

Figure 25 | ASTERISK study design – a randomized crossover study.

conditions shown as “Experimental” (myoelectric control with the liner and ASTERISK system) and “Control” (standard prosthetic device configuration). For the control condition, the subject will be using their everyday prosthesis. For the experimental condition, we will fabricate and provide a new socket to allow for the additional socket volume necessary for liners worn with the ASTERISK electrodes. Each subject will participate in both conditions of the study. The condition that each subject completes first will be chosen by a random number generator that also ensures block randomization with an equal number of participants assigned to each condition first in the test sequence using a custom program that was created under a prior research project.

Subjects will participate in four research visits and will take part in two, one-month long take-home periods. Some researchers have suggested that persons with transradial amputation require, on average, 3–5 weeks of training [22], while others have suggested that 5 hours of training is sufficient [23]. Therefore, we expect a one-month take-home period to be sufficient to allow users to become comfortable with each socket configuration while optimizing the take-home duration to maximize study efficiency.

Twelve subjects will be recruited for this study to allow for a 25% dropout rate and still ensure that we meet our goal of at least 9 subjects to achieve our desired statistical power level (described in the Statistical Plan below). Each subject will use their current prosthetic terminal device (e.g., prosthetic hand) with the experimental socket. If the subject normally uses a wrist rotator prosthesis, then LTI will provide one to be installed in their experimental socket. As described above, the OPUS-SD (survey) will serve as our primary outcome measure for this study, but we will also collect secondary outcome measures, including the Socket Comfort Score (survey), Prosthesis Evaluation Questionnaire (survey), AMULA, prosthetic wear time/usage, and elbow range of motion.

Participant Eligibility: All subjects must be current wearers of trans-radial myoelectric prostheses or orthoses, have used their prostheses/orthoses for at least six months, be between the ages of 18 and 89 years, understand spoken and written English (for the purpose of consenting), and not have any neurological or physical conditions which would prevent them from performing the experimental tasks. The risks to pregnant people and fetuses are unknown and therefore those who are pregnant should not participate in the study and will be screened by self-disclosure. Subjects in this study will not be discriminated against due to sex/gender or race/ethnicity. Potential subjects will be screened via telephone for eligibility for the study.

STUDY PROTOCOL

Visit 1: During the first visit, the subject will be consented and enrolled in the study. Measurements and casts will be taken so an experimental socket can be fabricated. Subjects will then be asked to complete the in-lab validated outcomes measures (OPUS-SD, PEQ, AMULA, elbow range of motion, SCS, etc.) as described above to provide a baseline measure of function and satisfaction with their usual prosthesis. If there is leftover time and the subject is not fatigued, this battery of tests may be repeated to help to reduce the learning effects associated with performing a new task. By having the subject practice these tests, learning effects will be reduced as they enter into the 2x2 crossover portion of the study. The 2x2 crossover design was specifically chosen to help mitigate the impact of learning effects related to the administration of outcome measures that are new to the test subjects by randomizing the order of conditions. Over the next few weeks following Visit 1, a study prosthetist will create the experimental socket with our ASTERISK system integrated into it. Once the experimental socket is fabricated, the subject will return for Visit 2.

Visit 2: Two to four weeks after Visit 1, subjects will return for Visit 2. During this visit, the subjects will first repeat the battery of outcomes administered in Visit 1 to both serve as the baseline of the 2x2 crossover portion of the study as well as identify test-retest variability in their results. The subjects will then be randomly assigned to a group to determine the order of test condition for that subject. If the subject is randomized into the experimental condition, they will be fit with the experimental socket with the installed ASTERISK technology. All subjects, regardless of test condition, will then receive training on controlling their prosthesis in their current test condition by the site occupational therapist (OT). The training will start with basic skills, including opening and closing the device, and grasping various shapes such as cone/cups, regular/irregular block shapes, and various size and weight balls. Then they will advance to splinter skills, involving partial completion of ADL tasks, for example, positioning the device on the handle of a large mug and gripping the handle. And finally, they will practice full task skills, i.e., grasping the handle of a large mug and bringing the mug up to the subject's mouth to drink from it, putting the mug back down, and releasing the grip. All subjects will also receive instructions on how to fill out the daily log (for the ensuing at-home portion of the study). For those starting with the experimental condition, instructions will be given on how to don, connect, and charge the ASTERISK sensors. Once they are comfortable using the device, they will be sent home with the experimental prosthesis.

One-Month At-Home (Condition A): Subjects will be asked to wear their experimental prosthesis and perform their daily activities either using their everyday socket (control condition) or socket with liner and ASTERISK sensors (experimental condition). An ActiGraph activity monitor (worn like a wristwatch; provided by the experimenters for use by the subjects) will be worn on the prosthesis to monitor prosthesis usage throughout the day. The ActiGraph contains an inertial measurement unit that records prosthetic lime acceleration, rotation and orientation. It does *not* record a subject's location. All subjects will be asked to keep a daily log to track any issues they have with their prosthesis and help identify and document any issues with real-world use of the device. Researchers will periodically check-in with the subject (by phone, text, email, etc.) to maximize adherence to the daily log, debug any technical issues, etc.

Visit 3: After one month, subjects will return for Visit 3. At this time the data will be downloaded from the ActiGraph monitor and the daily log collected. Subjects will perform the same in-lab testing as in Visits 1 & 2, with subjects performing the functional outcomes measures using the prosthetic control modality used in the prior month and providing feedback on the system via a custom survey developed as part of this effort. The test conditions will then be switched (those using the control condition in the first month will now use the experimental condition and vice versa) and subjects will receive training on the second test condition. For those switching to the experimental condition, instructions will be given on the use of the ASTERISK sensors. All subjects will be instructed and trained on their newly assigned prosthesis control condition by a study OT as described in Visit 2. Once trained, subjects will again be sent home to use the device in a real-world environment.

One-Month At-Home (Condition B): This is the same as the first one-month take-home session, except subjects have swapped conditions. All subjects will once again be asked to keep a daily log to track any technical issues. Researchers will periodically check-in with the subject to maximize adherence to the daily log, debug any technical difficulties, etc.

Visit 4: After one month, the subjects will return for Visit 4. This visit is the same as Visit 3. At this time the data will be downloaded from the ActiGraph monitor and the daily log collected. Subjects will perform the same in-lab testing as in Visits 1–3, with subjects performing the functional outcomes measures using the prosthesis control modality used the prior month and providing feedback on the system via the

custom survey that will include questions related to overall preference (control vs. experimental) as well as other pertinent feedback. Upon conclusion of the in-lab testing, the experimental socket will then be returned, and the subject set back up on their usual socket by a study prosthetist. At the end of this visit, the subject's participation in the study is complete.

Extra Visit(s): In certain cases, subjects may become too fatigued (physically or mentally) to complete the entire planned activity during the scheduled visit. Additionally, in some cases, equipment failures may delay completion of the activity planned for a visit. In such a case, subjects may be invited to return to complete the visit activity at the next mutually agreed date. If the return visit is due to equipment failures, subjects will be offered the standard travel stipend for the secondary visit.

STATISTICAL PLAN AND DATA ANALYSIS

Pilot Validation Study: A pilot study is defined by Moore, et al. [24] as a timely and cost-effective preparatory investigation intended to inform the successful design of future, often larger, clinical studies by testing study designs, measures, procedures, recruitment criteria, etc. The proposed pilot study is intended to mimic a future clinical trial and will be used to confirm our processes, including an assessment of the feasibility of our test protocols, recruitment and retention rates, etc. However, even more importantly, the pilot study is intended to provide outcomes data related to interparticipant and intraparticipant variance parameters from the target patient population for our primary and secondary outcomes. These data can be used in a robust power analysis that will determine the required sample size for a larger, follow-on clinical trial. In addition, this trial will allow us to confirm that our processes are sufficient for our planned data analyses or identify gaps that can be addressed before the initiation of the follow-on clinical trial.

While larger sample sizes can yield more precise estimates of confidence intervals and variance estimates, there are diminishing returns with larger samples sizes. These diminishing benefits often become outweighed by practicalities such as time and funding. Therefore, we will follow the recommendation of Moore et al. [24], as well as the power analysis described below, and include 12 participants to estimate average values and variances of our specific outcome measures in the target population. We recognize that this pilot study may not demonstrate definitive evidence for a treatment effect of the ASTERISK intervention. However, it provides a method that optimizes value and practicality to prepare for a definitive clinical trial to demonstrate the potential effectiveness of the ASTERISK system on prosthesis satisfaction and other secondary measures.

Power Analysis: We also performed a power analysis to evaluate the insights and conclusions that may result from the proposed take-home portion of the study. While many tests may be carried out in a particular study, Baguley [25] states that the power analysis should be conducted on the "principal hypothesis" to determine the sample size. Our principal hypothesis is that ASTERISK will increase prosthesis satisfaction when compared to standard socket configurations as measured by the Orthotics and Prosthetics User Survey (OPUS) – Satisfaction with Device (SD) measure. Two primary parameters are required to perform the power analysis associated with the proposed study design: the size of the difference in our primary outcome measure that we are trying to detect (δ) and standard deviation (SD) of the difference between two values for the same subject (σ). We aim to be able to detect a change that provides a minimum detectable change (MDC) on the OPUS-SD. Jarl et al., [16] reported that the minimum detectable change of the OPUS-SD was 15 points (δ). Other studies are currently using the OPUS to test the efficacy of an intervention on upper limb prosthesis performance. Dr. Matt Wernke at WillowWood is currently using the measure to examine the change in scores on the OPUS using the aforementioned MyoLiner. He was kind enough to share yet

unpublished data [26] in which he had observed a standard deviation (SD) of the difference between two values for the same subject on the OPUS-SD (σ) to be 12.2 points on 14 patients, when one outlier (as confirmed by Z-scores) subject's data were excluded.

A power analysis was conducted using the MGH sample size calculator software for cross-over studies [27] to determine the study population needed to reject the null hypothesis that the ASTERISK does not change prosthesis satisfaction as measured by the OPUS-SD. This calculation was performed with the assumptions that we are planning a study of a normally distributed, continuous response variable from a 2x2 cross-over of study subjects. Data described above indicated that the difference in the response of matched pairs is normally distributed with a standard deviation of 12.2. If the true difference in the mean response of the matched pairs is 15 points on the OPUS-SD, the calculation concluded that we would need to study 9 subjects to achieve the standard target of 80% statistical power. From the MGH calculator, with 9 subjects, the probability is 89 percent that the study will detect a treatment difference at a two-sided 0.05 significance level.

Subject Recruitment, Test Sites, and Sub-Populations: To account for potential subject attrition, we will recruit 12 subjects that are current wearers of trans-radial myoelectric prostheses to allow for a 25% dropout rate to ensure that we will reach our goal of 9 subjects completing the study. The 12-subject estimate from this analysis directly aligns with the 12-subject recommendation for pilot studies from Moore et al. [24] described above, and therefore we are confident that our proposed pilot study will allow us to generate valuable information to guide the design of future clinical trials.

Recruitment of more than a modest number of upper limb prosthetics subjects can be difficult. Therefore, planned subject recruitment has been distributed across three test sites: LTI (2 subjects), WPI (6 subjects) and Handspring Clinical Services (4 subjects), and can be redistributed as necessary. While the ASTERISK could have great benefit to users of other amputation levels, this pilot study will focus on trans-radial users to keep the population as homogeneous and focused as possible.

In addition to the three experimental sites visited by subjects, three other entities will participate in the project team. Debra Latour (Occupational Therapist; Assistant Professor, Western New England University) will provide occupational therapy on-site to subjects at all experimental sites. Elizabeth Newton (Newton Statistical Consulting) will provide data analysis and statistical consulting for the overall project. Lastly, faculty and staff from Nursing and Health Professions at University of Hartford will also provide prosthesis fabrication for the experimental work occurring at all three sites.

Secondary Measures: As described above, we performed the power analysis based on our principal hypothesis. However, we plan to do much more in depth and rigorous analysis of our 2x2 randomized crossover study data upon completion of data collection. We will also examine several other outcome measures such as elbow range of motion, AMULA scores, SCS scores, PEQ scores, and prosthesis wear time. Again, we recognize that this pilot study may not demonstrate definitive evidence for a treatment effect of the intervention. However, it will allow us to explore models that can be used in future clinical studies. In addition, we hope that the proposed experiments will generate variance data across the battery of additional outcomes measures that can be published to help future researchers plan their clinical studies.

Statistical Model: The primary statistical analysis will be led by Dr. Newton and will consist of the development of a generalized liner mixed model (GLMM) for crossover designs. In this 2x2 crossover study, 2 treatments will be administered in 2 periods and 2 sequences, as described above. We will employ a linear mixed model for this design as discussed in multiple references [28,29]. The model will contain

fixed effects for treatment, sequence, and period as well as random effects for subject and test site. Models with and without treatment carryover effects will be examined.

With 6 subjects in each treatment sequence group, the model, without covariates, is as follows: $y_{ijk} = \mu + \alpha_i + \beta_k + \tau_d + \lambda_c + d_{ij} + e_{ijk}$, where: i, k, d, c =1, 2; j=1, 2, …, 6; y_{ijk} is the response of the j^{th} subject in the i^{th} sequence and the k^{th} period; μ is the general mean; α_i is the sequence effect; β_k is the period effect; τ_d is the direct treatment effect; λ_c is the carryover effect (0 for period 1); d_{ij} is the random effect associated with the j^{th} subject in the i^{th} treatment sequence; and e_{ijk} is random error associated with the j^{th} subject in sequence i at period k. Additional terms in the model will include a random effect for test site (as testing will occur at LTI, WPI, U. Hartford and Handspring Clinical Services) to increase precision of the estimates. In a 2x2 crossover design, carryover effects are confounded with the other effects. We will examine models omitting each of the effects in turn to assess their contribution and we will consider the inclusion of a washout period between test conditions to better characterize these effects when finalizing the study design.

Statistical Analysis: Prior to fitting models, exploratory data analysis, including numerical and graphical summaries, will be conducted to examine distributions and check for outliers. In addition, plots will allow visual assessment of relationships between predictors and outcome. The fitted models also will be assessed by graphical and numerical means. Residuals will be examined for conformance to model assumptions. It is possible that transformation of some of the response variables may be necessary. Additionally, we will provide appropriate corrections for any sets of multiple comparisons during post-hoc analyses (e.g., Bonferroni-Holm) as required. We will work with our statistician, Dr. Elizabeth Newton, to design the study to get as much useful data out of a relatively small number of subjects as possible.

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