Protocol Title page

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Official Title: Effects of Temperature Control Liner Materials on Long-Term Outcomes of Prothesis Use

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The protocol has been approved by the responsible Institutional Review Boards. Study subjects are asked by the principle investigators to provide informed consent in accordance with human-subjects protection regulations.

Subjects: Subjects are recruited from the community at two sites, in Chester, PA, and Pittsburgh, PA. Inclusion criteria are the use of a prosthesis with liner suspension, at least one year of prosthesis use, a well-fitting socket, the ability to walk with the prosthesis outdoors without notable limitations (K-Level 3), stable weight, and absence of acute medical conditions that would temporarily affect the ability to use prostheses. Exclusion criteria are use of a non-standard liner size, known allergies against liner materials, and any inability to understand the protocol and to comply with the associated tasks, such as maintaining a log of days when the prosthesis could not be used.

Power analysis was based on the cross-over statistical methods above and previous literature and One-sided determination. Halsne, et al. [1], in an analysis of 12-month step activity data in participants with trans-femoral amputation reported that the average change in step activity scores for subjects in the hot and cold months of the year was significantly higher than in the moderate temperature months of the year corresponding to an effect size of 0.47. This effect size and a sample size of 50 subjects, results in 85% power to detect significant differences.

The assumed effect size would equate a difference in prosthesis utilization of four days per year if the average yearly number of days with prosthesis use has a standard deviation of 10 days. Irrespective of the statistical significance of such an effect, every day of work absence has a relevant economical effect to the employee and the employer.[2] Given the duration of the study and the potential reluctance of subjects to change their liner type, it is anticipated that up to 9

subjects (18%) do not complete the protocol, bringing the statistical power to 80%. Comparable prospective intervention studies in the past have utilized sample sizes between nine [3] and 20.[4]

A steady state within either of the interventions will be assumed [5], yet it will be possible to detect any baseline drift or seasonal fluctuations with the proposed repeated measures design. Previous studies have used a repeated measures design to investigate the reliability of outcome measures, such as the Locomotor Capabilities Index and the Two-Minute-Walk test [6-8]. The Prosthesis Evaluation Questionnaire (PEQ) has been validated in that fashion as well.[9]

Missing values are possible due to drop-out and intermittent non-compliance with the data collection schedule. This would not invalidate "year-on-year" comparison of the remaining data sets. Provided that baseline characteristics can be sufficiently described by existing data, it may also be possible to interpolate and extrapolate missing data points with some accuracy.

Despite the long duration of the data collection, the intervention itself will have a comparably low burden on the subjects' daily lives, which is expected to make participation appealing to a wide range of potential subjects who are targeted by online and offline postings.

Methods: The protocol utilizes a double-blind longitudinal cross-over research design. A sample of trans-tibial prosthesis users is randomly assigned to one of two groups. While subjects in one group receive PCM liners, the members of the other group are fitted with regular gel or silicone liners. After six months, the first group receives conventional liners (and turn their PCM liners in) and the second group receives PCM liners (Table 1). Prostheses in either group are equipped with activity monitors, and participants are asked to keep daily notes of any perceived issues with their residual limb or socket fit. In regular intervals, subjects' physical performance capabilities and prosthesis-related quality of life, including limb and overall health, is assessed using standardized methods.

Table 1: Schedule of enrolment, interventions, and assessments

	STUDY PERIOD					
	Enrolment	**Allocation**	**Post-allocation**			**Close-out**
TIMEPOINT	$-t_1$	**Jan 15 or Jul 15**	***Every 6 weeks***	***6 months***	***12 months***	***12 months***
ENROLMENT:						
Eligibility screen	X					
Informed consent	X					
Liner size determination	X					
Allocation		X				
INTERVENTIONS (Randomized sequence):						
PCM liner			⟷	⟷		
Placebo liner				⟷	⟷	
ASSESSMENTS:						
Demographics, Anthropometrics	X					
Two minute walk (2MWT) distance			X			X
PEQ Scores			X			X
StepWatch activity data			X			X

Comparing liners over the duration of six months allows detecting short- and long-term effects of the different approaches, including effects due to seasonal outdoor temperature changes, material abrasion and fatigue, and potential unsustainable material properties (i.e., diminished temperature control capabilities of the PCM). In order to cover a comparable portion of the year regarding climatic conditions, the protocol is started at one of two dates only: Mid-Winter (around January 15th) or Mid-Summer (around July 15th). Any possible washout period after changing liners is expected to be completed well within the first assessment intervals [10], so that unbiased data can be compared for all the listed assessment points for either liner.

Randomization is performed by the study statistician, using proc survey select available in SAS version 9.4. in a block randomization scheme with lengths of 2 and 4. Blocks length is unknown to the clinical personnel. This block design assures a balanced allocation in the groups and reduces the chance that testing personnel will be able to guess the next intervention group assignment. This, in turn, serves to minimize bias in participant allocation to the intervention group at the beginning of the study.

Upon entering the study, every subject receives two identical new liners that match their currently used one in size as measured by a credentialed prosthetist. The liner material is either the same as in their existing liner or PCM infused silicon, depending on group allocation. In order to blind the subjects and study personnel to the treatment, all study liners are custom ordered for each subject from the same manufacturer (Willowwood, Sterling, OH) in a uniform color and outer fabric design. The packaging is uniform as well apart from a label containing the study participant number provided at ordering. Every liner is imprinted with a unique serial number that is the only sign by which it can be identified as a PCM or conventional liner. The manufacturer provides a list of these numbers, which will only be accessed by research personnel

once the data collection and analysis procedures are completed, so that the results can be attributed to the proper group. Two identical liners are provided to allow subjects to alternate between them on a daily basis, which is recommended practice in order to allow cleaning and air drying liners and to maximize life time of the material. (A regular life time of six months continuous wear is common for prosthesis liners.[11]) Subjects are instructed to handle and rotate the liners in their usual way, in order to assure realistic test conditions, but are asked to not wear their previously existing liner for the duration of the study.

The prosthesis-related quality of life is assessed during this first appointment, using domains "About the prosthesis" (question group 1 of the PEQ[12]), "Specific Bodily Sensations" (group 2), "Ability to Move Around" (group 4), and "Satisfaction with particular Situations" (group 5). "Importance of different aspects" (group 7) is assessed as well, to provide insights for appropriate interpretation of responses. The PEQ contains a large number of questions that have been devised to cover all aspects of prosthesis-related quality of life. The explicit intention of the tool is to provide the option of customizing a questionnaire by selecting a subset of the PEQ questions, all of which are considered equivalent and are scored on an analog scale from 0 to 100.[13] The PEQ is valid for lower-limb prosthesis users, has high internal consistency (Cronbach's alpha = .73 – .89) and temporal stability over a mean retest period of 30 days (ICC = .79 – 90)[12]. The likewise administered two-minute walk test (2MWT) [7] has well established psychometric properties in lower-limb prosthesis users.[8] Of particular interest to the proposed study is the responsiveness of the 2MWT to rehabilitation in lower-limb prosthesis users.[7] Significant increases in total distance were found from initial prosthesis fitting (baseline) to discharge from rehabilitation, and at a 3-month follow-up.[7] A Stepwatch monitor (Modus Health, Washington, DC) is affixed to the ankle of the prosthesis and measure step counts over time.

This device has been utilized for a large number of research studies involving lower limb prosthetics [10, 14, 15] and meets the specifications issued by the Department of Veterans Affairs regarding outcome assessment technology.[16] Using the "Trex" evaluation algorithm, the device allows an assessment of user activity by considering ambulation energy, peak performance, and cadence variability indices.

In addition to determining liner sizes, subjects' height, weight, age, and time since limb loss are recorded at the first appointment.

Subjects are asked to continue their regular activities of daily life while wearing the new liner, and to make a note of any days during which the prosthesis could not be used due to residual limb health issues, as a redundancy to the step counter data. About every two weeks, a member of the research team will schedule a 5-minute appointment with the subject to read out Stepwatch data. Subjects are not required to come to the research site for the respective appointments, which may be scheduled at their homes or places of work according to subjects' preferences. While the Stepwatch monitor can store up to 50 days of data, two-week-intervals have been chosen to mitigate the adverse effects of possible equipment malfunction or application errors. Any adverse events or other unsolicited reports will be recorded as they occur.

Every six weeks, appointments are scheduled to conduct the 2MWT, complete sections "About the prosthesis", "Specific Bodily Sensations", "Ability to Move Around", "Satisfaction with particular Situations", and "Importance of different aspects" of the PEQ, and read out step data.

At the 6-month appointment, after completing 2MWT and PEQ, subjects turn in their two study liners and receive two new liners, representing the respectively other variety. Following a short rest, subjects will complete the 2MWT and PEQ once more before the test day is concluded while wearing the new liner.

The 12-month appointment marks the end of the data collection for this study. Individuals blinded to liner type will perform all data collection.

Subjects receive a compensation of $30 per site visit for a total compensation of $270. This payment schedule is intended to reduce the occurrence of drop-outs.

Outcome Variables: The main outcome variable is prosthesis utilization and is operationally defined as "total step count per time" and as the "number of days with prosthesis use per time". Prosthesis utilization is the clinically most relevant variable, as it describes the extent to which a person's limb loss affects their social and economic participation.[17] To determine the number of days of prosthesis use, self-reported information will be evaluated along with step count data. A day without substantial prosthesis use will be assumed if the daily step count is below the 20th percentile for the average daily step count of the respective individual over the full year. Only if both methods agree on the number of dates without prosthesis will the information be used for analysis in order to reduce the errors caused by inaccurate memory or by malfunctioning equipment.

Secondary outcome variables will be "Step count bouts per time unit", "Two-minute walk distance", "Prosthesis function rating", "Well-being rating", "Mobility rating", and "Satisfaction rating", the latter four of which are based on question groups 1, 2, 4, and 5 of the PEQ respectively. Analyzing those variables will allow a more comprehensive understanding of the effects of PCM liners and may inform the hypotheses of subsequent studies investigating their function mechanisms.

Depending on the eventual sample composition, it may be possible to extract incidental findings on the effects of demographic and anthropometric factors on measured outcomes with the

different liners. Any such results may be useful as pilot data for subsequent studies to further investigate the utility of PCM in prosthetics.

Several possible comparison variables are deliberately not included in this clinical trial. Monitoring changes in liner temperature or material properties during use would necessitate the use of additional data collection equipment, which would be likely to interfere with the regular use of the liners and thus pose a bias to the measured data. Also, it is unclear how temperature data should be interpreted (e.g., whether lower temperatures are always better than higher, or steady temperatures better than fluctuating) to become clinically meaningful. It is anticipated that the findings of the present study motivate subsequent research to investigate the function mechanisms of PCM liners and to better explain the results of this study.

Skin health, although an important outcome of prosthesis use, has likewise not been included in the study protocol. Assessment of residual limb skin health may help detect a number of adverse reactions to prosthesis use, ranging from skin abrasion to tissue necrosis. Measuring skin health outcomes results is fairly subjective and requires timely notification and assessment as skin issues occur. It is thus challenging to apply a reliable measure consistently across time, and especially across different research sites. This study focuses on prosthesis utilization, and considers skin and other health issue to have effects on the measured quality and quantity of prosthesis utilization. For the purposes of this research, the mechanisms that may lead to changes in that outcome variable are not the focus, and investigating them is therefore deferred to subsequent studies.

Statistical Plan and Data Analysis: Exploratory data analysis will be conducted prior to formal statistical analysis. The distributions of all key variables will be examined to check for data errors and ensure that modeling assumptions are not violated. Numerical summaries including

means, standard deviations, medians and histogram graphical techniques will be used for continuous variables and frequencies will be computed for categorical variables.

Patterns of association between descriptive measures (i.e., demographic and diagnosis characteristics) and intervention outcomes will be examined using paired t-tests, chi-square tests with Fisher's exact, correlation analyses (and regression analyses, as appropriate). From these analyses, critical demographic and clinical characteristics will be identified that will be controlled for in the statistical models and incorporated into the design of future controlled clinical studies. Data will be analyzed according to study group membership regardless of study completion. However, missing data patterns will be examined and reasons described for attrition and missing data because such patterns may be informative for identifying systematic biases in future studies. The Kolmogorov-Smirnov test will be used to verify the normality assumption and if it is violated appropriate transformations will be considered. Correction for multiple testing will be by adjusting p-values using the Benjamini-Hochberg method. Prior to formal statistical analysis, data will be compared across treatments to check if they are comparable. If differences exist, baseline demographic effects will be taken into account in mixed effects models. The correlation among repeated measures will be examined and adjusted appropriately such as unstructured, confound symmetry, or auto-regressive.

Outcome data are collected at baseline, 1.5-month, 3-month, 4.5-month, and 6 months and repeated at the 2nd half-year. The effect of intervention, time, and group*time interactions will be evaluated. Baseline data for key variables will be compared between randomization groups, and if they are different, a random intercept mixed effect will be used. Mixed effects modeling techniques will be used for the repeated measures. Since mixed effects models do not assume a balanced design, subjects who do not have data (dropouts) on all 10 time points will still be

included in the analysis (intent to treat). It will be tested if scores for the intervention are significantly different from the control condition's scores.

Possible additional analyses include a more detailed investigation of prosthesis utilization over time by comparing seasons, months, weekdays, or hours of day within and across interventions. [1] Furthermore, it may be possible to analyze covariates that predict prosthesis utilization, including anthropometric and demographic data.

Data management and analysis utilizes a secure network and computer system to protect confidential data with security measures established by the HIPAA Security Rules. The data collected are verified, edited, and updated to provide clean data for analysis. Once data pass all the edit procedures, analytical data sets will be created for analysis by a statistician. As a final step in quality control and an initial step in analysis, descriptive statistics will be calculated and graphic displays created.

List of Abbreviations

2MWT – Two Minute Walk Test

HIPAA – Health Insurance Portability and Accountability Act of 1996

ICC – Intraclass correlation coefficient

PCM – Phase Change Material

PEQ – Prosthesis Evaluation Questionnaire

SPIRIT – Standard Protocol Items: Recommendations for Interventional Trials

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