Title: [1771535-1] Evaluation of Software Generated Customized Foot Orthoses

Protocol Version Date: 24 August 2021

1) Objectives

Purpose of the Study:

The purpose of this study is to determine whether custom-made foot orthoses generate a significant decrease in the perception of pain among individuals with foot pain and/or pathology.

Secondary:

1. To determine whether custom-made foot orthoses generate a significant increase in comfort among individuals with foot pain and/or pathology.

2. To determine whether custom-made foot orthoses improve quality of life among individuals with foot pain and/or pathology.

2) Background

Foot orthoses, or orthotics, are prefabricated or custom-made devices that are inserted into shoes to alleviate load and provide cushioning of feet. Prefabricated foot orthoses are also known as "over-the-counter" orthotics and are mass-produced. Custom-made foot orthoses are contoured to an individual's feet [1].

In general, literature has not been consistent in determining the ideal way in which foot orthoses should be customized and fabricated. Results of studies comparing the effectiveness of prefabricated versus customized foot orthoses show very heterogeneous results, created a large gap in literature. Thus, the current evidence on this subject is quite limited, especially when analyzing the effects of foot orthoses in people without pathologies, since evidence in this group is even scarcer [2, 3].

Foot orthoses have proven to be useful in pain management [4, 5, 6, 7], in non-contact injuries [8, 9] and in overuse pathologies in distal and proximal segments of the lower extremities, as well as in their prevention [10, 11, 12]. In a study that assessed pain in patients with rheumatoid arthritis and forefoot pain, the use of custom-made foot orthoses significantly decreased forefoot pain while walking [13]. In another study comparing custom and non-custom-made foot orthoses, forefoot pain was found to be better relieved by custom-made orthoses than the standard ones [14]. Custom-made foot orthoses can be tailored to specific foot pathologies, as in pain reduction due to the increase in soles pressures in patients affected by rheumatoid arthritis, hallux abductus valgus and secondary metatarsalgia [7]. Custom-made foot orthoses were also useful in shifting pressure

off painful areas in patients with intermetatarsal bursitis, reducing pain and disability, which was supported by ultrasound findings [15].

The literature has been consistent in pointing out the positive effects of foot orthoses on comfort in the short term. For example, studies such as that of Tarrade et al [16] found significant improvements in the pain of workers who remained standing for long periods of time when using foot orthoses. However, the medium to long term evidence for this is still not very clear. Among the scarce evidence on this subject, García-Hernández et al. [17] demonstrated that manufacturing workers showed greater comfort after a period of adaptation, which occurred between one and two months after starting the use of foot orthoses. Carrying out this process, using modern, tailor-made manufacturing systems could mean better results, as these methods have proven to be the most effective in generating foot orthoses.

Though the shape of people's feet varies from person to person, currently typical shoes have inside standard foot orthoses that do not provide customized designs to fit the differences in shape of the foot of each person who uses them. This generates a wide range of loading and pressure distribution along the sole. This can generate pain and a reduced quality of life in the people who use them. Today we have the possibility of designing foot orthoses tailored to each person's foot, which generates a support and impacts absorption according to the shape of one's foot, which would allow us to generate greater comfort and thus avoid discomfort and injuries caused by the alteration of the loads.The goal of this study is to find out whether the use of software generated custom-made orthopedic foot orthoses improves pain in the long term.

3) Inclusion and Exclusion Criteria

The attending orthopaedic foot and ankle surgeons will identify patients based on clinical exam and/or radiographic findings. Screening and eligibility will be conducted by the research coordinator.

Inclusion Criteria:

1. Foot/ankle pain or pathology OR diagnosed pes planus, pes cavus, pronator foot, supinator foot, metatarsalgia, Morton's neuroma, sesamoiditis, hallux valgus, intermetatarsal bursitis.
2. Between 18 and 65 years of age
3. BMI is greater than 18.5 or less than 30.

Exclusion Criteria:

1. Individuals who have had surgery in the lower limbs during this past year.
2. Individuals who already have custom-made orthopedic orthoses.
3. Patients with active diabetic ulcers or chronic foot pressure ulcers.

4) Study Timelines

We aim to enroll up to 60 participants over the course of 1-3 months. Each participant will be evaluated at baseline, when the customized foot

orthoses will be made, and the corresponding tests will be conducted. Subsequently, consecutive surveys will be carried out at 0, 7, 30, 120, and 360 days. days from the first day of foot orthoses use to measure the change in pain and comfort with use of the foot orthoses. An interim analysis will be conducted after all subjects have completed the 30-day time point. This interim analysis will allow us to determine whether subjects are using the foot orthoses they have been provided. Complete primary analyses is estimated to be completed within 3 months after the termination of the study.

5) Study Endpoints

Primary endpoint: Successful patient use of a 3D printed custom orthotic for at least 6 months and up to 1 year

6) Secondary endpoint: Improvement in patient report outcomes after the use of a 3D printed custom orthoticProcedures Involved

The evaluation will have a duration of approximately 30 minutes, which consists of four stages:

a. Collection of personal data and anamnesis: The patient's demographic data, anthropometric measurements and anamnesis will be consulted.

b. Physical examination: Visual and palpatory inspection of the foot.

c. Baropodometry: Taking of plantar pressures by means of a platform.

   i. Static: Subjects should remain standing on the platform measuring plantar pressures for 15 seconds with arms at the sides and looking straight ahead. There is only 1 sample.

   ii. Dynamic:

      1. Walking: Subjects should walk over the pressure measurement platform. Five shots per foot, with a protocol of 5 steps to reach the platform.

d. Hindfoot photography: A photograph of the hindfoot will be taken, which allows us to measure the angulation of the hindfoot.

Making and Delivery of Foot Orthoses:

During a period of 2 weeks, the foot orthoses will be created using Soleit software which will later be manufactured via three-dimensional printing.

Use of Foot Orthoses:

Foot orthoses will be sent to participants along with a small instruction manual and protocol of use. When using the foot orthoses for the first

time, participants must navigate to a specific link to begin monitoring their foot orthoses use. The link will be sent prior to receiving the foot orthoses. Participants should use the foot orthoses progressively for a period of 1 week. The first week will be an adaptation week in which participants should use the foot orthoses for 1 hour on the first day, then increase use by 1 hour each day until reaching 4 consecutive hours at which time the foot orthoses can be worn continuously.

Follow-Up and Questionnaires:

Participants will be sent surveys on three occasions—0, 7, 30, 120, and 360 days from the start of use of their foot orthoses. The survey will primarily evaluate a 9-item scale that measures the comfort generated by the foot orthoses. The survey completed at day 0 and 30 will serve to evaluate the comfort of the foot orthoses. The survey sent on day 7 will be used to evaluate the tolerance of the new foot orthoses.

- Pain Visual Analog Scale (VAS) – Rates the intensity of pain from 0 – 10 with 10 being the worst pain possible.
- EuroQol 5D – Rates the quality of life including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The scale ranges from 0 to 100, with 100 indicating the best health imaginable.
- Foot Health Status Questionnaire – Measures foot pain and function, general foot health, and perception of footwear. The scale ranges from 0 to 100, with 100 indicating the best foot health.

Adverse Events:

Because this study is subjective in nature, only adverse events that are serious, unexpected, and device-related will be recorded. Collection of adverse events will begin once subject begins using the foot orthoses. All adverse events will be monitored and reported in accordance with the UC Davis Institutional Review Board (IRB) policies.

7) Data and/or Specimen Management and Confidentiality

☒ I understand that if this study involves the use of the UC Davis Health Electronic Health Record (EMR/EPIC) also contains the clinical data for Marshall Medical Center (MMC). I understand that MMC patient data cannot be accessed for research purposes and that I must take the necessary steps to ensure that MMC data is not accessed, used, or disclosed for UC Davis Health research purposes.

☒ I undersand that if this study involves use of UC Davis students' educational records (including records in the PI's own possession such as course exams/assignments), I must consult with the Registrar's office to see if all requirements of the Family Educational Rights and Privacy Act (FERPA) are satisfied.

Data Analysis & Statistical Considerations:

A quasi-experimental, within-subject (repeated measures) and longitudinal controlled design will be established. Patients will be recruited from the patient population at the University of California, Davis Orthopaedic Foot and Ankle Clinic. From the total number of enrolled subjects who meet the inclusion criteria, an optimal N of 52 subjects will be randomly selected, considering a medium effect size (0.4) and a p less than 0.05 to achieve a statistical power of 0.8. Being a longitudinal study, a sample loss of 10% was established. Therefore, 60 subjects will be included in the study. We aim to enroll up to 60 participants over the course of 1-3 months.

Intra-subject pain, comfort, and quality of life averages pre-use and post use of the foot orthoses will be compared. The sample of participants will be described with central tendency statistics and baseline parameters, and post use evaluations (0, 7, and 30, 120, and 360 days after first foot orthoses use) will be established. These will be compared to study possible differences. For normally distributed dataions, repeated measures,one-way ANOVAnova for paired samples will be used for normal distributions will be used with a Tukey's post-test and in case of non-normal distributions, Friedman's test will be used with a Dunn's post-test. All analyses will be performed with the SPSS statistical package.

Privacy, Data Storage & Confidentiality:

All study data, such as forms, reports, and other records, including electronic records, will be identified by a coded number to maintain patient confidentiality and will only be accessible by members of the research team. Paper records will be kept in locked file cabinets in locked rooms. Electronic data will be located on computers containing a log-on and password. Written permission from the participant must be obtained prior to the release of clinical information, except as necessary for monitoring by the IRB. All communication, consent procedures, forms, and storage of patient data will be maintained and stored in accordance with the UC Davis' IRB, Good Clinical Practices requirements, and the Health Insurance Portability and Accountability Act. All personnel involved with the study are required to complete the Protection of Human Subjects training.

Due to the complexity of the software, it will only be used by a trained kinesiologist belonging to the Soleit team.

Although the evaluating kinesiologist will have access to all the volunteers' data temporarily in order to carry out the correct control and follow-up work, three independent databases will be maintained to guarantee the confidentiality of the information:

a. Identification data: Data allowing identification of patients will be kept in Excel listing, handled by the study investigators.

b. Biomechanical data: The data corresponding to pressure measurements, medical history and images are essential for the automated design of the foot orthoses and will be managed anonymously, without any participant identifiers, in the Soleit software.

c. Tracking Data: Tracking forms for recording the effectiveness of the foot orthoses will be managed independently via surveymonkey.com and will be anonymously transmitted, without any participant identifiers, to the principal investigator after which the surveymonkey.com service will be cancelled, and the data deleted.

At the end of the evaluation, all data will be anonymized and delivered to the researcher responsible for statistical analysis.

8) Data and/or Specimen Banking

Address the last bullet point if you answered "Yes" to tissue banking within the Initial Application Form.

If data will be banked for future uses address the following questions:

- *What data will be banked?*
- *What identifiers will be included in that data?*
- *For what purpose will the data be used?*
- *Where and how will data be stored?*
- *How long will the data be stored?*
- *Describe the procedures to release data, including: the process to request a release, approvals required for release, who can obtain data or specimens, and the data to be provided with specimens.*

9) Provisions to Monitor the Data to Ensure the Safety of Subjects

As this is a minimal risk study, no data and safety monitoring (DSMB) will be used. Microsoft Excel will be used to manage data used. Sponsor will conduct an ongoing monitoring of study conduct and safety data.

The following will be reported within 10 calendar days, except when 24-hour reporting is specified:

1. Information that indicates a change to the risks of potential benefits of the human research:

a. An interim analysis, safety monitoring report, publication in the literature, or revised investigator brochure that indicates an increase in the frequency or magnitude of a given harm, uncovers a new risk, or provides more information about the benefits of the human research.

b. Change in FDA labeling or withdrawal of the device from the market.

c. Protocol deviation that harmed participants or indicates participants might be at increased risk of harm. If the protocol deviation was made in

order to eliminate an apparent immediate hazard to a participant, the PI must submit the information within 24 hours.

d. Complaint of a participant that indicates participants or others might be at increased risk of harm or at risk of a new harm.

2. Any adverse event experienced by a participant of other individual, which is both unexpected and at least probably related to the human research device.

a. A harm is "unexpected" when its specificity and severity are not accurately reflected in the consent document.

b. A harm is "at least probably related" if the research device more likely than not caused the harm.

c. Timeline Exception: If the unexpected and at least probably related harm is death of a research subject, the PI must report the information within 24 hours.

3. Finding of Non-Compliance or Allegation of Non-Compliance.

4. Protocol Deviations: Failure to follow the protocol due to the action or inaction of the investigator or research staff. Exception – If the protocol deviation was taken in order to eliminate an apparent immediate hazard to a participant, the PI must report the information within 24 hours.

5. Breach of confidentiality: must be reported within 24 hours.

6. Change to protocol taken without prior IRB review to eliminate an apparent immediate hazard to a participant: must be reported within 24 hours.

7. Complaint of a participant that cannot be resolved by the research team.

8. Unanticipated adverse device effect. Exception – if the unexpected and at least probably related adverse device effect results in the death of a research subject, the PI must report the information within 24 hours.

All data collected will remain confidential. Data will be stored securely under the patient's study identification number. All clinical data, images and surgical/procedural data will be de-identified prior to any in-house or public presentation of data or images. Coded data will only be released to those listed as study investigators or support staff. Paper data records will be stored in locked file cabinets in a locked office. All electronic research data will be stored on the PI computer that is password protected and encrypted.

IRB, FDA and any applicable regulatory agencies will have access to the study records upon request. The data and associated identifiers will be kept for up to 5 years in a locked research facility accessible only to designated personnel, at which time the data will be destroyed per hospital policy. If the results of this study are published, the data will be reported

collectively without mention of any subject's identity, thereby ensuring subject anonymity.

10) Withdrawal of Subjects

Subjects may withdraw from the study at any time. Subjects may be withdrawn by an investigator if the participant does not participate in study follow-ups. Research staff will document the reason for withdrawal. Subjects who fail to appear at initial visit or do not receive the foot orthoses will be considered screen failures and will be removed from the study and the study data.

11) Risks to Subjects

Risk Assessment and Device-Related Risks:

Discomfort:

A conceived device-related risk is that the foot orthoses cause discomfort. This will be controlled in two ways. The first is that the use of the foot orthoses will be done progressively. This means that participants should use the foot orthoses for 1 hour on the first day, then increase use by 1 hour each day until reaching 4 consecutive hours at which time the foot orthoses can be worn continuously. Any discomfort should be reported to the nurse practitioner in charge and will be reviewed to assess if a new foot orthosis with the appropriate modifications should be made or if the use of the foot orthoses should be discontinued.

Blisters:

Another conceived device-related risk is the generation of blisters due to friction. If a participant is found to experience an area of increased rubbing that could lead to a blister, the participant should discontinue the use of the foot orthoses immediately. In addition, as a part of protocol, participants should inspect the soles of their feet when they finish any type of physical activity and check for any areas of redness as a result of the use of the foot orthoses. If any redness is present, inform the nurse practitioner who will assess if new foot orthoses with the appropriate modifications should be made or if the use of the foot orthoses should be discontinued.

12) Potential Benefits to Subjects

Participants will receive custom-made foot orthoses free of charge. No additional compensation will be received.

13) Sharing of Results with Subjects

N/A Results will not be shared with patients**.**

14) Provisions to Protect the Privacy Interests of Subjects

As part of the consent process, the patients will be informed about the nature of the data that will be collected, how the information will be collected and who will have access to the information and how it will be stored. The information will be handled initially by the clinical and research team at the collecting institution and only shared with the data hub institution UC Davis in a deidentified format.

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15) Economic Burden to Subjects

The only anticipated cost is transportation to the clinic during the initial visit. There will be no cost to the subjects for the manufacturing of the foot orthoses. The non-standard of care foot orthoses will be paid for by Soleit.

16) Drugs or Devices

If the research involves drugs or device, describe your plans to store, handle, and administer those drugs or devices so that they will be used only on subjects and be used only by authorized investigators. N/A

☐ I confirm that all investigational drugs will be received by the Investigational Drug Service (IDS). The IDS will store, handle, and administer those drugs so that they will be used only on subjects and be used only by authorized investigators.

☐ I confirm that all investigational devices will be labelled in accordance with FDA regulations and stored and dispensed in such a manner that they will be used only on subjects and be used only by authorized investigators.

17) Review Requirements

Are there any contractual obligations or other considerations that require IRB review of this research, or review at intervals other than those required by the Common Rule or FDA? If yes, check box:

☐ Yes

☒ No

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