Human Subjects Protocol

VA Puget Sound IRB

Improving the Detection, Classification and Treatment of Misaligned Arthritic Ankles

MIRB # 00967

NCT03440008

Funding Agency: Department of Veterans Affairs

Principal Investigator: Joseph M. Iaquinto, PhD

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Abstract

Objective(s) and Hypotheses:
Osteoarthritis (OA) is a degenerative joint disease which severely limits mobility and is associated with moderate to severe amounts of pain and discomfort. Ankle OA is strongly associated with a prior injury (vs. "wear and tear" which is more common at other joints). Prior injuries to the bones surrounding the ankle joint may cause the joint to become misaligned over time, and the cartilage surfaces to wear abnormally fast – likely contributing to OA.

The motion of the bones at the ankle joint (and therefore their alignment) is very difficult to measure. Clinically, a static (non-moving) standing x-ray is used to diagnose the presence and severity of ankle misalignment; however this does not capture misalignment during movement which may result in missed opportunities for diagnosis and early intervention with non-invasive treatment.

This study has three aims:

1) measure bone motion and alignment using an x-ray technique that captures bone motion in 3D during walking (dynamic measurement with our biplane fluoroscope)

- Hypothesis 1: During gait, there are different tibio-talar kinematics between OA participants with static varus alignment, OA participants with static valgus alignment, and controls.

2) determine if the single static clinical image technique is accurate enough to diagnose ankle misalignment 100% of the time, and completely capture the severity of misalignment

- Hypothesis 2: Some static neutrally aligned OA participants will exhibit varus or valgus tibio-talar misalignment when measured dynamically using biplane fluoroscopy.

3) determine if an inexpensive medical device, a shoe insert (wedged orthotic) is capable at restoring alignment.

- Hypothesis 3: OA participants with static (varus/valgus) tibio-talar misalignment will exhibit reduced misalignment when walking with (lateral/medial) wedge insoles.
- Hypothesis 4: OA participants with static neutral alignment, but with dynamic (varus/valgus) tibiotalar misalignment will exhibit reduced misalignment when walking with (lateral/medial) wedge insoles

Research Design & Methodology:
Up to 120 participants with ankle OA (up to 40 with varus misalignment, up to 40 with valgus misalignment, up to 40 with neutral alignment) and up to 30 participants without ankle OA will be enrolled. Participants will be men and women, age 18-80 years, who are able to stand and walk for at least one hour without significant difficulty. Participants will undergo a series of radiological measurements including: a standard x-ray from the hips down, a set of x-rays of the legs, a CT scan from the knees down, up to 80 fluoroscopic images while walking or

standing. Participants will do the fluoroscopic trials with and without wedged shoe insoles. The radiological measurements will be used to address the aims outlined above.

At the end of this study we hope to: (1) have a better understanding of ankle arthritis, (2) be able to demonstrate the potential for an improvement upon the current clinical examination for ankle misalignment and/or OA, and (3) provide evidence for, or against, the use of shoe inserts to manage and/or treat ankle misalignment and/or OA. It is hoped that this work will aid future clinicians and researchers in delaying or preventing the onset of ankle OA in at-risk veteran and non-veteran patients.

List of Abbreviations

Provide a list of all abbreviations used in the protocol and their associated meanings.

AE – adverse event

CT – computed tomography

mSv - millisievert

OA – osteoarthritis

ROP – report of other problem

SAE – serious adverse event

UW/HMC – University of Washington/Harborview Medical Center

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1.0 Key Study Personnel

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2.0 Introduction

The National Arthritis Data Workgroup that the 27 million US adults had clinical OA in 2008,[1] with about 6% of the US population afflicted with ankle OA.[2] In active duty military service, the rate of OA incidence is 7.86 cases per 1,000 person-years.[3] Extremity and specifically ankle OA has been seen at a higher rate in Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) compared to previous conflicts.[4] Concerning veterans, a VHA Support Service Center (VSSC) database search of local and national outpatients yielded the following table of ankle OA cases locally and nationally for 2014.

ICD - 9 Code	Entire VA	V20	Seattle VA
(715.17) Primary Ankle OA	1,087	186	21
(715.27) Secondary Ankle OA	300	31	2
(715.37) Unknown Primary / Secondary Ankle OA	7,165	258	175
(715.97) OA not Ankle Specific	8,434	334	102
(716.17) Traumatic Arthropathy of the Ankle	2,155	64	14

The majority of ankle OA is associated with post-traumatic injury.[5-7] Incident rates for ankle sprains in the military have been reported at 45.14 per 1000 person-years between year 2000 and 2006;[8] and at 34.95 per 1000 person-years in records between 1998 and 2006.[9] Post-traumatic ankle injuries include: ankle fractures, recurrent ankle instability and single sprains with continued pain.[6, 7] The type of fracture is directly correlated to the incidence of OA: with increasing Weber fracture classification, there is an increase in OA incidence.[10]

The average latency time between ankle trauma and end-stage OA isapproximately 20.9 years.[11] The mechanical stability of the ankle joint following fracture is essential to healthy function.[12-14] Varus

misalignment of the hindfoot has been correlated with lateral ankle sprain or chronic lateral instability.[15] It is important to note that misalignment is not only associated with prior trauma, of patients with primary (non-traumatic OA), 50% had no reported foot deformity, but 22% had cavovarus foot shape and 13% had planovalgus foot shape.[7] These findings suggest that misalignment (traumatic or non-traumatic) may lead to OA over time.

Misalignment of the hindfoot can be observed in radiographic views of the supramalleolar, tibio-talar (intra-articular), and inframalleolar aspects.[13] For the purposes of this proposal, tibio-talar misalignment is the focus. In a study of 406 ankles, 55% had varus alignment, 37% had neutral alignment and 8% had valgus alignment (normal alignment defined as between 90-99 degrees, varus alignment as less than 90 degrees and valgus alignment as 100 degrees or greater)[7]. In end-stage ankle OA patients, average alignments of 88.8 degrees(63–110 degrees) have been found, with 49.0% of cases having a varus malalignment, 50% within normal and 1% as valgus alignmen.[11] These studies show that varus misalignment has a significant presence in ankle OA, and is an important clinical diagnostic measure.

Joint-preserving surgeries (osteotomies of the tibia) have been explored to delay or prevent arthrodesis or arthroplasty by correcting alignment.[16-18]; but conservative treatments also exist. Wedged insoles have been found to increase subtalar joint valgus moment in knee OA patients,[19] and to alter ankle eversion and eversion moment.[20, 21] These studies suggest that wedged insoles could be used to modify the kinematics and kinetics of the ankle joint, potentially to a beneficial effect in ankle OA patients. However, it should be noted that all of these studies were studies are unable to distinguish between subtalar and tibio-talar joint motion. This proposal's use of biplane fluoroscopy directly addresses that shortcoming.

3.0 Specific Aims and Hypotheses

Clinically, tibio-talar alignment is assessed through static weight bearing radiographs – however, stance is functionally very different than gait and the tools to capture dynamic bone motion are not readily available in clinical settings. In research, optical motion capture (a technique that uses reflective markers and infrared cameras to track position and motion) is often used to study gait, however its ability to measure dynamic bone motion and position, in this case tibio-talar alignment, is limited. Biplane fluoroscopy is a radiographic technology that can track the talus, and thus measure dynamic ankle alignment. Importantly, some neutrally aligned ankles (determined via static radiographs) may actually exhibit misalignment during gait (dynamic biplane fluoroscopy). Treatment of misaligned ankles with conservative strategies (e.g., wedged insoles) may reduce misalignment, slowing the rate of OA development. We seek to quantify dynamic ankle misalignment in OA patients, detect a possibly hidden dynamically misaligned patient population, and explore how both populations respond to a conservative treatment approach.

Specific Aim 1: To investigate ankle kinematics in controls and participants with OA.

Hypothesis 1: During gait, there are different tibio-talar kinematics between participants with OA and static varus alignment, participants with OA and static valgus alignment, and controls.

Specific Aim 2: To identify dynamically misaligned ankles in participants with OA who are currently classified as neutrally aligned using static analysis.

Hypothesis 2: Some participants with OA and static neutral alignment will exhibit varus or valgus tibio-talar misalignment when measured dynamically using biplane fluoroscopy.

Specific Aim 3: To evaluate the potential of lateral or medial wedging to restore alignment in participants with OA and misaligned ankles.

Hypothesis 3: Participants with OA and static (varus/valgus) tibio-talar misalignment will exhibit reduced misalignment when walking with (lateral/medial) wedge insoles.

Hypothesis 4: Participants with OA and static neutral alignment, but with dynamic (varus/valgus) tibio-talar misalignment will exhibit reduced misalignment when walking with (lateral/medial) wedge insoles.

4.0 Resources and Personnel

All data collection procedures for this study will be conducted at the VA Puget Sound in Seattle, WA. See Study Staff Sheet attachment for listing of personnel, ability to obtain consent, and access to PHI.

Under the supervision of the PI, designated study staff will be responsible for conducting recruitment, consent and scheduling study procedures. The PI, Investigators, and/or Research Engineers will conduct procedures with participants. The PI, Investigators, and the Biostatistician will be primarily responsible for data analysis and interpretation; Research Engineers may also assist with this. Under the supervision of the PI, the Program Coordinator is responsible for IRB related matters.

5.0 Study Procedures

5.1 Study Design

Participants in this research study will be men and women, age 18 to 80 years, who are able to walk without the assistance of an aid. People with and without ankle OA, will be enrolled. Targeted enrollment by ankle OA status and alignment type is listed in the table below. Vulnerable populations will not be specifically targeted for enrollment. See inclusion/exclusion criteria below in section 5.4.

Study Groups	Varus Misalignment	Neutral Alignment	Valgus Misalignment
up to 30 – Controls, no ankle OA	0	30	0
Up to 120 - People with Ankle OA	40	40	40

See section 5.5 below for data collection procedures and risk management.

5.2 Recruitment Methods and Initial Screening

Up to 3000 individuals may be approached during recruitment and enrollment procedures. Please note that all references in this section to in-person contact/initial-screening will follow the *Talking Points* attachment, all phone calls for contact/initial-screening will follow the *Phone Script* attachment, all references to approach letters and postcards refer to the *Recruitment Letter* attachment.

Recruitment activities at the VA

CPRS and Letter/Phone/In-person

Designated study staff will screen the relevant VA Puget Sound (Seattle and American Lake) clinic lists and attend clinic at the VA Puget Sound facilities to identify potential participants with a qualifying ankle OA diagnosis. Before or after clinic, study staff will discuss with the clinician any patients that might be appropriate candidates. If the clinician agrees that the patient may be an appropriate study participant, the clinician will ask the patient if she/he is interested in speaking with study staff; patients will be given a chance to opt out. For patients who are interested, study staff will speak to potential participants directly during or after a clinic visit and/or use CPRS to obtain potential participants' contact information (i.e., name, address, telephone number). For potential participants who learned about the study in person, study staff may make a follow-up approach phone call and/or send an approach letter to potential participants asking whether they are interested in finding out if they are eligible for the study. If potential participants are unable to meet with designated study staff in person then we will send an approach letter to them asking whether they are interested in participating. We may also search CPRS to identify individuals with a qualifying ankle OA diagnosis and mail them the approach letter. If potential participants have not spoken with us within 30 days of the first call and/or mailing the approach letter, study staff will contact them by phone up to two more times about this study. The approach letter will also include an "opt out" postcard. The opt-out postcard will have a unique study recruitment identification code of the form "IDCTd1", "IDCTd2" etc. where the letters IDCT are an abbreviation for "Improving the Detection, Classification and Treatment", the letter d indicates the contact information came from the database, and the

appended number is based on the order in which the postcard was mailed. If an individual returns the postcard to opt out they will not be approached about this study again.

Database and Letter/Phone/In-person

Designated study staff may also identify potential participants using the VA Center for Limb Loss Prevention and Prosthetic Engineering Subject Registry (PI: Klute, #00433). The Registry contains contact information for participants who were screened for and/or participated in previous studies with our research group and agreed to be contacted for future studies. Study staff may make an approach phone call and/or send an approach letter to potential participants asking whether they are interested in the study. If potential participants have not spoken with us within 30 days of the first call and/or of the mailing the approach letter, designated study staff will contact them by phone up to two more times. The approach letter will also include an "opt out" postcard. The opt-out postcard will have a unique study recruitment identification code of the form "IDCTr1", "IDCTr2" etc. where the letters IDCT are an abbreviation for "Improving the Detection, Classification and Treatment", the letter r indicates the contact information came from our Registry, and the appended number is based on the order in which postcard was mailed. If an individual returns the postcard to opt out they will not be approached about this study again. Designated study staff may also speak with participants in the registry about this study during a clinic visit if an individual has an appointment at the VA.

The link between the study recruitment identification code and individuals' contact information will be kept in a password protected electronic document at the VA Puget Sound (Seattle) in a restricted access folder. Hard copies of screening documents will be labeled with the ID code and stored in a locked cabinet at the VA Puget Sound.

Print/Text/Online/Flyers/Newsletter

We may post classified ads in print and online publications *(see Recruitment Ad Text attachment)*. We may also post the classified ad text to our Center's webpage.

We will also post flyers *(see Recruitment Flyers)* at the VA Puget Sound (Seattle and American Lake) so that interested potential participants can contact us about the study. The flyers will also be presented/posted via the VA's closed caption TV system. We may also post flyers in publicly accessible locations in the community such as public library community boards, community center information boards, and coffee shops.

We may also include recruitment information in our center newsletter.

VAPSHCS Research Week

Designated study staff will host an information table during the VA Puget Sound Healthcare System Research Week. Study flyers and informational posters will be posted at the information table. If study staff identify any Research Week attendees as potential study participants, they may approach

the attendee about participating in the research study. If the attendee is interested in learning more about the study, study staff may screen the attendee for qualifying criteria.

Recruitment Activities at UW/Harborview

A confidentiality agreement will be obtained for this activity; the UW does not consider itself "engaged" for the recruitment activity described below, please see attached engagement worksheet.

Designated study staff will screen relevant UW/Harborview clinic lists, appointment calendars and patient medical records to identify potential participants with a qualifying ankle OA diagnosis. Study staff will also attend clinic at these facilities to identify and/or contact potential participants. Before or after clinic, study staff will discuss with the clinician any patients that might be appropriate candidates. If the clinician agrees that the study may be a good fit for a patient, the clinician will ask the patient if she/he is interested in speaking with study staff. For patients who are interested, study staff will speak to potential participants directly during/after a clinic visit to tell them about the study, give them a study flyer, and/or request their permission to screen them for initial eligibility (via the VA IRB approved In-Person Talking Points) and provide this information to the VA. If potential participants are screened for initial eligibility in person using the In-Person Talking Points, study staff will label the noted responses with a recruitment id code and no HIPAA identifiers or sensitive health information will be noted on the form. Study staff will transport the forms to the VA for storage. If patients are interested in learning about the study and/or in doing the initial screening but are unable to meet in person with study staff, we will look up the patients' contact information in their medical record and contact them on the phone and/or send them the VA recruitment letter (the VA IRB approved letter with VA contact information would be sent per the process described above). Staff will also search/access UW medical records to identify individuals with a qualifying ankle OA diagnosis, obtain their contact information (i.e., name, address, telephone number) and mail them the approach letter.

Also, for potential participants who were initially contacted via letter and/or in-person but have not yet completed the initial screening, study staff may provide the potential participants' contact information and limited pre-screening criteria over the phone to other study staff at the VA who will enter it into the screening log for tracking and follow up. This information may also be added (via VA remote access) to the screening log maintained on the VA server. Study staff will follow up with potential participants based on the VA approved protocol. Consent and all data collection procedures will be conducted by approved research staff at the VA Puget Sound.

5.3 Informed Consent Procedures

A waiver of informed consent and HIPAA authorization will be used for recruitment and screening purposes. A waiver of documentation of consent and HIPAA authorization will be used to in order to retain the preliminary eligibility screening responses *(see Talking Points and Phone Script)*. Informed consent will be obtained prior to enrollment in the study.

Designated study staff and/or the PI will conduct the informed consent process. All study personnel will complete the necessary human subjects' protections training per VA policy.

5.4 Inclusion/Exclusion Criteria

Our targeted range for the total number of study completions is up to 150.

Inclusion Criteria:

Control participants without OA: up to 30

1. age 18 to 80 years
2. able to stand and walk for about an hour (with breaks) and at least 15m (about 50ft) at a time without difficultly

Participants with ankle OA: w/varus ankle (up to 40); w/neutral ankle (40); w/valgus ankle (40)

1. radiographic evidence of tibio-talar ankle osteoarthritis (osteophytosis and/or joint space narrowing)
2. age 18 to 80 years
3. able to stand and walk for about an hour (with breaks) and at least 15m (about 50ft) at a time without difficulty

After consent, unless usable images are available, all participants will have a set of X-rays (foot and ankle, and long leg x-ray) in order to determine final group assignment and eligibility.

Exclusion Criteria: all participants

1. prior ankle joint replacement or fusion, or recent (<1 year) surgical, neurological, rheumatologic, or lower limb musculoskeletal problem (e.g., current foot ulcer, severe hip/knee OA, terminal illness, etc.) that impairs an individual's ability to do the walking tests
2. required use of upper extremity gait aid or orthotic device for walking
3. rapid onset of ankle OA (<3 years) following ankle fracture
4. diagnosis of severe ankle instability or deformity such as pes planus or knee varus / valgus deformity, visible during exam or present in long leg radiograph
5. inadequate cognitive function or language proficiency to consent or to participate
6. current incarceration
7. body mass index (BMI) > 40 kg/m2
8. once an alignment type in the OA group (varus, neutral, valgus) has been filled, further potential participants of that population will be excluded
9. currently pregnant

Additional Exclusion Criteria, Controls only:

1. Ankle pain or ankle OA in addition to the above exclusionary criteria

5.5 Study Visits, Data Collection, and Risk Management

All data collection procedures will be performed at the VA Puget Sound. There are several components to the study. Participants may be asked to complete some or all components of the study depending on their eligibility, but may do so over several visits (up to 4). We anticipate that most participants will complete all study components within 3 visits over a 3-4 month timeframe, but particpant schedules and the accessibility of facility resources (i.e., the ability to schedule time slots with the Dept. of Diagnostic Imaging) may extend the study timeframe beyond this estimate. We will attempt to conduct multiple components of the study during each visit in order to minimize the number of visits required for participation. Visits may last up to 5 hours each. Study visits will be scheduled by contacting the participants on phone, or during in-person contacts. We may contact participants with appointment reminders via email or phone.

During study sessions, visitors and observers will not be allowed in the lab unless the participant agrees to their presence; the participant can change her/his mind at any time.

Photos and video

We will also take video and photos of participants during portions of this study for documentation and use in research publications. All videos and photos will be taken from the neck down (to avoid facial identification) and without sound (to avoid voice identification), and tattoos and other distinguishing marks will be covered to protect the identity and privacy of our participants.

Eligibility Screening and Group Determination

Participants will have been preliminarily screened during recruitment, then during the first visit, after informed consent is obtained, we will make a final elibility determination. This will include verifying that the information collected during recruitment is accurate and current.

At each visit that involves exposure to radiation female participants of child-bearing potential (under age 50) will undergo a pregnancy test (urine test) so we can verify that they are not pregnant. Designated study staff will escort female partipants to the bathroom and provide them with a specimen cup, pregnacy test strip, and a disposable container on which to place the used test strip. Staff will go over the test instructions, and verify the test result. Staff will not handle urine specimens, we will tell particpants how to handle and dispose of the materials. If the test indicates that the participant is pregnant she will be not be able to participate in the study and we will advise her to see her regular clinical care provider. If a participant cannot continue in the study they will still be compensated for the visit.

Particpants with ankle OA will be grouped based on their clinical diagnosis of ankle coronal plane alignment (varus, neutral or valgus) as noted in their medical record, and/or determined by reviewing/measuring ankle alignment in x-rays in the medical record during recruitment and screening. Participants with ankle OA who do not have a formal clinical diagnosis of alignment type, if

alignment type cannot be determined via the x-rays on file, or if there are no x-rays on file, will be categorized after undergoing the Standing Long Leg X-ray.

Participant weight and height will be measured, and his/her age, sex, race/ethnicity and Veteran status will be recorded. Participants will be asked to walk in a straight line in the hallway while a researcher times the subject to determine his/her natural walking speed.

Medical Record Review

If participants have a VA or UW medical record we will check to see if they have already had a CT scan and/or X-rays (images) that can be used for this study. If participants report that they have had a CT scan and or X-rays at a different medical facility we may request copies of them. If possible, we will use the previously collected images for our data set and analyses so that participants do not have to be exposed to additional radiation. We will also access participants' medical records (at the VA Puget Sound or UW/Harborview Medical Center) to collect information related to their foot and/or ankle diagnosis and related clinical treatment. If participants' medical records are not at the VA they will be asked to sign a release form so that we can obtain copies of these records. After the release has been signed and delivered, the CT scans, X-rays and any other requested clinical notes from outside the VA will be delivered via the following methods:

- The images and other clinical treatment information may be burned to CD(s) or DVD by HMC or other facility and mailed to us via traceable shipping.

- A designated study staff member will pick up the CD(s) or DVD from HMC/UW or other facility and transport it to the VA.

- Information about lower extremity diagnoses and clinical treatment may be provided to designated study staff over the phone – the information will be labeled with the participants' study code and added to study records.

Radiologic Measurements

Over the course of the study, participants will not be exposed to more than 0.47 mSv of radiation; we will expose participants to the lowest amount of radiation possible to achieve the aims of the research. For comparison, this total dose is less than a quarter of the exposure for a single head CT scan. Participants will be permitted to take breaks as needed.

Standing Long Leg X-ray

If needed, this component will be performed at the VAPSHCS Department of Diagnostic Imaging. Paricipants will stand still while a frontal X-ray of the hips down is taken. This will allow us to quantify

the alignment at the hip, knee and ankle. We will also take standard foot alignment X-rays, including anterior/posterior and medial/lateral views of the feet.

We will measure the ankle alignment, if a participant is determined to have an ankle alignment type for which the study group is already full, that individual will not be able to participate further in the study, but will be compenated for the visit.

Please note, for participants that do not have a clinical diagnosis of alginment type (those with and without OA), we do not intend to inform them if we note misalginment. It is unknown at this time if ankle misalignment is causitive to the development of ankle OA or if it is clinically relevant to prevention or conservative treatment of OA; these are some of the questions that this study hopes to address. Therefore, the information would not be useful to participants.

The CT scan and Biplane Fluoroscope session will be conducted in no particular order and may be conducted over multiple visits.

CT Scan

If needed, this component may be performed at the VAPSHCS Department of Diagnostic Imaging or using the CLiMB's LineUp weightbearing CT scanner. Participants will have a CT scan taken; the scan will start at the mid-tibia (lower leg) and extend down to include the feet and ankles. For scans taken in the VAPSHCS Department of Diagnostic Imaing, participants will be seated in a small plastic frame, on the CT scanner flatbed, with both feet resting against a flat plate; the plate will apply 10% of the participants' body weight to each foot during the scan to simulate partial weight-bearing. The LineUp CT scanner is designed so that subjects can stand and naturally be weightbearing, so no frame is necessary. The CT scan will be used to generate a computational model of the subject's bony anatomy – a necessary step for generating results with the fluoroscopy system.

Biplane Fluoroscopy – Baseline

While wearing shorts (their own or ones we provide), participants will change into standard lab shoes and enter the Biplane Fluoroscopy Laboratory. Participants will step onto an elevated walkway, which is flat, about 3-feet wide, level, and has handrails on both sides. They will be asked to walk freely up and down the walkway to get comfortable with the test environment. External markers may be placed on the shoe for tracking purposes. While participants stand still on the platform, two fluoroscopes will capture simultaneous X-ray images of the participants' foot of interest, to record the standing position of the foot bones. These dual fluoroscopes allow for tracking of the bone motion in three dimensions (3D) while participants walk. Next, participants will be asked to walk along the platform while simultaneous X-ray images of the foot of interest are taken; each X-ray exposure is expected to last about 0.5 seconds, and will image from about 3 inches above the ankle to below the bottom of the shoe or foot. This set of standing and walking trials may also be

conducted with a neutral insert in the shoes, or barefoot. With some pariticipants, we may capture images of each foot during the standing and walking X-ray procedures.

Biplane Fluoroscopy – Wedged Insoles

Research staff will insert one of the wedged insole configurations (selected based on the participants' varus/valgus indication) into both of the participants' shoes. Participants in the control group may be asked to do these procedures with several different insole configurations. Participants will then repeat the standing trial, and then perform walking trials in the same format described above. With some participants, we may capture images of each foot during the standing and walking X-ray procedures. Participants will be instructed to let us know if they feel pain or discomfort during the procedures. If the shoes or inserts feel uncomfortable, we will attempt to re-fit them, if we are unable to achieve a comfortable fit, we will stop the procedures.

We will not ask participants to walk through our active fluoroscopic imaging system more than 80 times total during the entire study, and as noted above the total radiation exposure for the study will not exceed 0.47 mSv.

Biplane Fluoroscopy Laboratory / Radiological Imaging Session – If needed

If for any reason we are unable to capture all of the fluoroscope or radiologic images we need during the prior visit(s), or if we found any problems with the images afterwards, we will ask participants to come in for an additional session to repeat or complete procedures as needed.

Registry

Participants will be asked if they are interested in joining our Center's Subject Registry (MIRB# 00433). This registry is used to recruit for studies being conducted by our Center. If participants choose to join the registry they will sign a separate consent form. Data about their foot/alginment type that is collected under this study will be added to the Subject Registry; this will help us determine which studies may be a good fit for participants in the future.

Repository

Participants will be asked if they are interested in allowing their study data to be added to our de-identified data repository so that it may be used for additional research in the future. Participants who are interested will be asked to sign a separate consent form for the repository (MIRB# 00493).

Additional use of de-identified data

Throughout the course of the study we will place a copy of all de-identified data in publicly accessible online data repositories. Once posted, the de-identified data will be publicly accessible to search, retrieve, and analyze for any purpose. Participants will be made aware of this use of de-identified data during the consent process and it wil be described in the consent form. If participants do not

wish to have a copy of their de-identified data placed in online repositories they can choose not to participate in the study.

Payment to Participants

Participants will be paid $25/hr for each study visit. Participants that attend the first visit but are screened out will be compensated for that visit. Payments may be issued in cash or check (participant preference). Checks will be mailed about 6-8 weeks after each visit, or cash payments can be collected through the agent cashier at the VA Puget Sound approximately 6-8 weeks after each visit.

Risks and Risk Management

Procedures Involving Radiation Exposure

There is a very small increased risk of cancer due to the amount of radiation exposure involved in this study. Based on previous Radiation Safety Applications by our research group, and using conservative estimates, the estimated radiation exposure is from two sources (**a**) the CT scans of subject anatomy, and (**b**) the fluoroscope imaging and (**c**) x-rays of static limbs, including long leg x-ray. For risk (a), the CT imaging is conservatively estimated to expose participants to 0.2 mSv of ionizing radiation and for the fluoroscopic exposure (b) an estimate (again conservative) of 0.20 mSv for 80 gait trials and (c) an estimate of 0.07 mSv. The total estimate of exposure is 0.47 mSv. For comparison, this total dose is less than a quarter of the exposure for a single head CT scan. Further, the upper limit of radiation exposure involved in this study is apprximately 1/7th of the estimated naturally occurring background radiation exposure (of 3.1 mSv) (http://hps.org/documents/) "Background Radiation Fact Sheet." For additional comparison, the EPA (https://www.epa.gov/radiation/radiation-sources-and-doses) estimates of annual radiation exposure is 6.20 mSv (3.1 mSv from naturally occurring background radiation and 3.1 mSv man-made sources such as equipment used in medical procedures), this study will therefore expose participants to ~7.5% of the annual background radiation. Please note that this is the maximum anticipated exposure, in practice we find that participants normally complete their walking trials in well under 80 attempts, but we wish to be conservative with our estimate. We will minimize the risk due to radiation by taking the minimum number of fluoroscope trials needed to obtain the necessary data. This means that some participants may only require 30 trails (potentially less), which will reduce the total radiation exposure. It is anticipated that most participants, particularly controls, will be well under the 80 exposures we have budgeted for in our radiation estimate. Existing x-rays and CT scans will be used whenever possible.

It is possible that participants may be exposed to loud noises (like a heavy door slamming) when they are inside the building that houses the biplane fluoroscopy lab; this may startle some individuals. The building where lab is located also houses a blast machine. The blast machine is located in a separate lab, diagonally across the building from the biplane fluoroscopy lab. The blast machine can be quite loud when standing directly outside of the door of the lab where it is located, however when walking to or when inside the fluoroscopy lab the noise sounds like a muted bang/door slamming. We have a

set of standard operating procedures that will be followed in order to minimize the risk that participants will be exposed to noises from the blast machine. The SOPs include escorting participants at all times and informing them of the potential noises prior to entering the building.

It is possible that participants could trip and fall during the walking procedures. The the biplane imaging walkway is clear of obstacles and is level, dry, and rigid. Thus, walking on the biplane walkway is akin to walking on a well-maintained sidewalk. The biplane walkway also has support railings on both sides; these railings will be within easy reach of participants at all times. Participants will also have time to familiarize themselves with the shoes and the area in which they will be asked to walk.

Participants may feel a mild level of emotional stress if they find it inconvenient to travel to the VA for study visits, or if they have difficulty sitting or standing still during the x-rays or CT scan. Participants will be instructed to let us know if they would like to take break during procedures, and they can opt out of the study at any time.

Inflicted Insight

It is possible that we could discover that female participants are pregnant. It is also possible that the imaging procedures (CT scans, X-rays and fluoroscopic images) could reveal that a participant has a serious health problem or anatomical abnormality (e.g., bone cancer). Potential participants will be screened during the telephone call, or in person screening, regarding their willingness to be made aware of the pregnancy test result and/or potential health problems discovered by the imaging procedures. Those who are not willing to be told about this information will be excluded from the study. Additionally, in the consent form, participants will again be made aware of this possibility and given the option to decline participation in the study if they choose. If a participant is determined to be pregnant and/or if we see an unexpected abnormality in a participant's radiological images we will advise them to follow up with their regular health care provider.

Wedged insole comfort

It is possible, although unlikely due to the brief nature of the data collection trials, that participants may experience discomfort or pain while standing and walking with the wedged insoles or study shoes. If this occurs it would likely be discovered immediately at the start of testing for a given wedge condition. Participants may experience mild soreness or soft tissue irritation (e.g., a blister) from walking with shoe inserts and/or in shoes that are unfamiliar, either during or shortly after the study sessions. Participants with ankle OA may experience a small increase in ankle or foot pain during or shortly after the study sessions. Participants will be instructed to inform us if they feel discomfort or pain and the procedures will be stopped so that we can adjust/re-fit the shoe/insole. If we are unable to achieve a comfortable fit the study session will be ended. Care will be taken to properly fit the shoes. Participants can take breaks at any time.

Quality Control

The PI will ensure the study procedures are being properly followed by keeping the research staff well informed of the current study procedures through regular/ongoing contact and meetings. The PI and/or designated research staff will verify visually that the data are sufficient and accurate as soon as possible after each data collection visit is complete.

Privacy and Confidentiality

See section 7.0 below for Information Security, Privacy and Confidentality related procedures.

5.6 Data Analysis

Plan and Hypotheses:

Hypothesis 1: During gait, there are different tibio-talar kinematics between OA participants with static varus alignment, OA participants with static valgus alignment, and controls.

> Linear mixed effects regression will be used to test for differences in gait kinematic measures coronal plane alignment being the primary dependent variables by OA group (clinical OA varus, clinical OA valgus or controls, the independent fixed effects). Study subject will be modeled as a random effect. If the omnibus test for association between gait kinematic measure and OA group is significant, then pair-wise comparisons will be carried out.

Hypothesis 2: Some static neutrally aligned OA participants will exhibit varus or valgus tibio-talar misalignment when measured dynamically using biplane fluoroscopy.

> To determine the potential miss-categorization of OA neutrally aligned participants: frequencies, percentages and 95% confidence will be estimated for the number of participants in the OA static (from standing radiograph) neutral group who are classified into varus, valgus or neutral using dynamic measures (from fluoroscopy trials).

Hypothesis 3: OA participants with static (varus/valgus) tibio-talar misalignment will exhibit reduced misalignment when walking with (lateral/medial) wedge insoles.

> Linear mixed effects regression will be used to test for improvement in misalignment, i.e. the reduction in coronal plane disparity between OA and control participants (the dependent variable) when walking with a wedge vs. no wedge (the independent fixed effect) for OA varus and OA valgus participants separately. Subject and subject-x-wedge interaction (the latter to account for variability across multiple trials in the difference in within subject misalignment by wedge use) will be modeled as random.

Hypothesis 4: OA participants with static neutral alignment, but with dynamic (varus/valgus) tibio-talar misalignment will exhibit reduced misalignment when walking with (lateral/medial) wedge insoles.

This will be tested using the same methods as Hypothesis 3, substituting OA varus and valgus participants (from static radiographs) to those who are neutral in static radiography, yet varus or valgus dynamically.

Additional Analyses:

1) Ankle misalignment likely varies during gait, and the pose of the foot during peak misalignment may not correlate with the position of the foot in the clinical 2D X-ray. To investigate this, the peak misalignment (varus or valgus) during gait as measured from the talar surface angles and talar tilt in data set 2 will be compared to the peak from the static standing fluoroscopic, this will be done for all groups. The result will be a measure of how frequently current clinical measure captures true maximum misalignment during gait.

2) The methods used to generate data set 2 can be used to re-create any 2D position from the 3D kinematics. Considering additional analysis 1, we may identify a phase of gait that more reliably demonstrates maximum misalignment (e.g. at heel rise). At the peak misalignment during that phase, we will generate additional simulated 2D X-ray images, in perspectives which would be possible to capture diagnostically (e.g. straight AP views and minor variations). In these new views, we will re-measure the talar surface angle and talar tilt. Such an exploration requires no additional subject X-ray exposure, as it is a digital processing of the data already collected. The result may be a 2D X-ray imaging angle / foot pose combination which is better suited than current methods for detecting maximum misalignment. This information may have immediate clinical benefit and will be rigorously pursued with additional study.

3) In a similar vein, we will perform a sensitivity test on the current clinical imaging methods. We will generate a series of 2D X-ray image planes by varying the standard clinical AP X-ray perspective in 1 degree increments about the SI and ML axes. Talar surface angle and talar tilt will be recalculated for each of these perspectives. By replicating this measure over a range of ± 15 degrees, we will determine the sensitivity of the clinical measure to foot positioning during diagnostic imaging.

The preceding three additional analysis serve to determine: (1) the ability of current methods to determine peak misalignment, (2) if a clinical angle / pose exists that is more diagnostically meaningful, and (3) the sensitivity of positioning to the current clinical method.

4) Transverse alignment of the ankle joint is technically more challenging to diagnose due to the need of such an superior / inferior image to pass through the tibia. With the methods described above, we can perform these measurements without difficulty. Using a similar regression and criteria as in Hypothesis 1, we will evaluate differences in transverse plane alignment during gait. Additional measures will compare the changes in malleolar / talar dome side spacing and the closest approach of the transverse borders of the malleoli to the talus. This may identify abnormal transverse wear patterns within the ankle joint – a measure that will not only benefit prevention, but that has significance in ankle replacement.

5) We will use a similar regression as in Hypothesis 1 to determine if there are differences in gait kinematic measures between OA varus / valgus (from static radiograph) and OA varus / valgus (from fluoroscopy trials). This will indicate whether these groups exhibit similar kinematics during gait, despite different static diagnostic determination.

6) We may find participants who do not benefit from wedge insoles (non-responders), depending on both the presence and size of these subgroups; this will yield pilot data to support identifying and investigating these subgroups in follow up proposals.

Power:

Our study is powered from a pilot study of ankle alignment during static phases of gait.64 Refer to Figure 3-6, Left: OA participants (group 1, 30 participants with 3 trials per subject, n=90) vs. Plot 1, Right: controls (group 2, 20 participants with 3 trials per subject, n=60).

Power analysis for coronal plane misalignment: Assumptions: mean = -1.8 degrees SD=1.8 degrees n=90 (30x3) for an OA group, and mean=1.7 degrees, SD=2.9 degrees, n=20 for the controls64 (valgus or varus) with 3 trials per subject and within subject error of 1.5 degrees. Based on 5000 simulated datasets and performing the mixed regression model described in H1, there is >99% power to detect the difference between groups, i.e., 3.5 degrees, as statistically significant, at p=0.05.

Coronal alignment is the measure that yields ankle varus, neutral or valgus. This demonstrates an appropriate sample size for the effect size of ankle alignment. Additionally, the pilot study did not differentiate between varus or valgus alignment. Due to demographics, it is possible that all six participants were varus or neutral. We suspect that cleaner separation of groups for comparison will only improve our ability to detect significant differences between groups.

5.7 Withdrawal of Participants

This is not a treatment study; withdrawing or being terminated from this study will not have an impact on participant safety. A study clinician or the PI may withdraw a participant without their consent if he or she feels that it is not in a participant's best interest to continue in the study or if they are unable to complete the study procedures. All data previously collected from participants who withdraw, or are withdrawn, will be kept and may be used in the study data analysis. Participants may withdraw at any time by informing the Research Coordinator and/or the PI.

6.0 Reporting

All safety information on Adverse Events (AEs), Serious Adverse Events (SAEs), unanticipated events or problems, and protocol deviations will be collected. This information will be collected at study visits and whenever participants call to report a problem. It will be collected on VA IRB forms (Report of a SAE and/or Problem Form), or Report of Problems (ROP) Form. Safety data will be collected on an as-needed basis and will begin upon enrollment into the study. Any anticipated AEs will be recorded

on a log sheet and reported annually with the CRQ. Although the risks identified in this study are relatively minimal, we will tabulate a list of any such reports that occur during the study and compare it with corresponding data available in the literature. This will allow us to analyze how much of an increased risk was due to the administered protocol. Also please note, the anticipated maximum radiation dosage (0.47 mSv) is far below any dose that would have a measurable effect on participants. After each report of an AE, SAE or an unanticipated problem, we will evaluate study procedures for previously-assessed risks, and will determine whether any changes to the protocol are necessary to minimize risks. The study will be suspended until these changes have been fully implemented and approved by the IRB.

If we become aware of relevant findings or information that may affect participants' health or welfare we will contact participants by phone and/or a letter to notify them.

7.0 Information Security, Privacy and Confidentiality

As with most studies, it is possible that a loss of privacy or confidentiality could occur. Given the impresonal nature of the majority of the data that will be collected, the risk of harm is minimal. Electronic data with PHI/sensitive information will be stored on the secure server at the VA Puget Sound. These data will only be accessed by authorized study personnel. Hardcopies of VA sensitive data and documents with PHI will be stored in a locked file cabinet in a locked office at the VA Puget Sound (Seattle). Study files/data with PHI or sensitive information will not be sent off-site. This is a locked facility to which only study investigators have access. Identifiable data will not be transmitted, transported, or stored on portable media or laptops outside of the VA, and the data will only be accessed by authorized VA study staff. We will notify the Information Security Officer of the location of the hardcopy data/files via the Data Inventory form. If study data is improperly used or disclosed we will notify the ISO and Privacy Officer within one hour of becoming aware of the issue.

Study data will be labeled with a study assinged code and de-identified data sets (data without any of the 18 HIPAA identifiers) will be created/used when data is made publically available and transmitted without restriction. The key to the code will be stored seperately from the study data and only designated VA study staff will have access to it. The key will be stored in a permissions restricted folder on the VA network. Study records with PHI/PII will be destroyed using VA approved procedures and in accordance with the records retention schedule after the study is completed; this will be a minimum of 6 years after the study has been completed. De-identified data with study assigned codes will be stored indefinitely. If participants choose to participate in the Subject Registry information about their foot/alignment type will be stored indefinitely in the Registry.

The CT scan and X-rays taken at the VA, which will contain the participant's name in the header, will be stored in the participant's medical record (CPRS), as per VHA Handbook 1907.01. The X-ray and CT data will be downloaded onto CD(s) by the Department of Diagnostic Imaging, and hand-transported by study staff to our data processing computers at the VA. CT scans and X-rays released to the VA

from the UW, or any other facility, via the VA Release of Information Form will be transported from the UW by study staff and/or mailed to the VA. Prior to any analysis of the X-ray or CT data, all patient and institution identifiers will be removed from the headers of the radiograph files, and replaced with the study-unique code. When the de-identified copy of the X-ray and CT data is properly created, it will then be uploaded from the CD(s) to our computer workstation for further analysis. The CDs/DVDs will be stored in a locked cabinet in a locked office when not being processed. We will take the CD containing PHI to our VA IT manager to be destroyed. At no time, will copies of any medical image data containing patient identifiers be placed on any computer. The fluoroscopic images will be identified from the onset with the study code only (i.e., no PHI). Electronic transmission of de-identified fluoroscopy images will occur between the Biplane Fluoroscopy Laboratory data collection computer and the data processing computers in a different room at the VA. The de-identified images/data will also be kept indefinitely.

De-identified, non-sensitive electronic data with the study assigned codes (described above) and all 18 HIPAA identifiers removed or converted to de-identified format, may be stored on non-networked equipment at the VA Puget Sound (computers/laptops/sd cards). These devices are stored in locked areas. De-identified data files will be sent off-site to our biostatistician (VA research staff) Jane Shofer, MS, and to our off-site collaborators Duane Storti PhD and David Haynor PhD. De-identified electronic data will not be encrypted. De-identified data files will be sent via email and/or other electronic media (CD/DVD, thumbdrive via hand delivery or trackable mail) to our biostatistician and off-site collaborators. These non-sensitive files may also be transported on thumbdrives or non-networked laptops by staff working at both the VA and UW. De-identified data may be transmitted by email between study investigators and collaborators here and at UW and will not be secured. These data will be stored and used on electronic media.

De-identified data (as described above) will be stored and publicly accessible to search, retrieve, and analyze. Participants will be informed, via the consent form, about this additional use of data.

Any consented photography or video will protect participatnts' identity because they will not include the participant's face or voice and they will be anonymized/edited during data collection or processing to remove or obscure any identifying features (such as scars and tattoos); and then the original file will be deleted. The video camera and the recording media (e.g., SD cards, optical disks) will be stored in a locked office at the VAPSHCS. Photos and videos that do not contain identifiable information may also be stored on password-protected computers/laptops for future use in scientific presentations and publications. These de-identified data will not be encrypted.

If participants choose to enroll in our data repository, a copy of their de-identified data will be placed in the repository and kept indefinitely.

8.0 Communication Plan

N/A – This is not a multi-site study.

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