Supplementary Appendix

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Title: Personalized gait retraining for medial compartment knee osteoarthritis: a randomized controlled trial

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Participant Characteristics

Table S1: Representativeness of study participants.

Category	Description
Condition	Medial compartment knee osteoarthritis
Special considerations related to:	
Sex and gender	62% of individuals with osteoarthritis are women.[1] The prevalence and incidence of osteoarthritis are 1·69 and 1·39 times greater, respectively, in females compared to males.[2]
Age	The prevalence of osteoarthritis increases with age, with <10% prevalence in individuals from 40–49 and 50% in those over 80.[2]
Race and ethnicity	78% of individuals with osteoarthritis in the US identify as non-Hispanic White, 10% as non-Hispanic Black, and 7% as Hispanic.[1] Within their own race/ethnic groups, non-Hispanic Black and Hispanic populations have higher rates of osteoarthritis than those who identify as non-Hispanic White.[1]
Geography	Prevalence of knee osteoarthritis varies by country. Prevalence is similar in rural and urban areas.[2]
Other considerations:	Higher BMI is a risk factor for the occurrence and development of knee osteoarthritis.[2]
Representativeness of this trial	60% (41 of 68) of the participants in this trial were women, which aligns with the known higher incidence for knee osteoarthritis in women than in men. The majority of the patients enrolled identified as White (79%, 54 of 68), reflecting the demographic of knee osteoarthritis. Individuals who identified as Black were slightly underrepresented in this trial, while those who identified as Asian were overrepresented. This different demographic distribution partially reflected the general demographics of the San Francisco Bay Area, where the study took place. We excluded individuals with BMI>35 from the study because of their inability to undergo MRI examination. Fourteen percent of individuals with osteoarthritis have BMI>35,[3] so the conclusions of this study may not directly apply to this group of knee osteoarthritis patients.

Protocol Summary

Here we summarize the trial procedures. The initial protocol, final protocol, and changes to the protocol, as documented in the grant, clinicaltrials.gov, and the Institutional Review Board protocol are in later sections of the Supplementary Appendix. This section summarizes these documents and the Methods section of the manuscript to provide a comprehensive and concise description of the interventions, trial procedures, and participant interactions. The protocol described here and in the Methods is accurate to how the trial was conducted, and thus, these sections supersede any information in the grant, clinicaltrials.gov, and the Institutional Review Board protocol in the event of a minor discrepancy.

Outcomes and Statistics
Outcomes and statistical considerations are described in the Methods section of the manuscript and the Statistical Analysis Plan at the end of this document.

Inclusion Criteria
Inclusion and exclusion criteria are described in the Methods section of the manuscript and in Figure 1.

Advertisement
We advertised for the trial through physician referral, flyers in local hospitals and clinics, presentations at local senior centers, and advertisements in print media. Most participants learned about the trial through the print-media advertisements. Advertisements described that individuals with medial knee pain from osteoarthritis who could walk for at least 25 minutes may be eligible to participate in a study that taught them a personalized walking pattern.

Screening
Individuals interested in the study completed an eligibility questionnaire by phone or using an online REDCap[4,5] form. This screening questionnaire assessed all inclusion and exclusion criteria, except those that required x-ray, MRI, or gait analysis, which were evaluated in subsequent visits. This is the first time that medial knee pain on the numeric rating scale was evaluated. Every pain assessment was administered with the following text read to the participant: "What was the usual or typical pain level in the medial compartment of your knee over the last week on a scale of 0 to 10, with 0 being no pain at all, and 10 being the worst pain you can imagine?"

Both the phone screen (which was read verbatim to participants) and the online screen included text describing study involvement, including duration, the number of visits, and major trial procedures, including gait analysis, gait training, x-ray, and MRI.

X-ray visit
Individuals who were both interested and eligible then visited the Palo Alto Veterans Affairs Hospital to learn more about the study, provide informed consent, complete another pain assessment, and receive an x-ray. A member of the study team read the following description of the study to the interested participant:

> "The purpose of this study is to compare the effectiveness of different types of walking training for individuals with knee osteoarthritis in the medial compartment of the knee. We and others have shown that training to walk consistently with a personalized foot progression angle, or how much you toe-in or toe-out [demonstrate with feet], is a promising non-surgical intervention for medial knee osteoarthritis over the course of a few months. However, it is still unknown what the best foot angle for walking training is and if the training is effective over a longer period of time. In this study, we are investigating the effects of different types of walking training on knee pain, knee joint loading, and cartilage health measured by MRI over the course of one year. Participants are randomly assigned to one of two groups; the only difference between the groups is which personalized angle the participant is trained to walk at. Today we will assess your knee pain and take an x-ray to confirm the presence of osteoarthritis. The remaining visits will happen at Stanford, between the Human Performance Laboratory for 12 walking training visits and the Lucas Center for two MRI visits. Briefly, participants walk on a treadmill with reflective markers on their body. There are two visits that we will use to choose the personalized foot progression angle followed by 10 walking training visits, where individuals get 'biofeedback', or buzzes like those from a cell phone, teaching them to walk consistently with their personalized angle. At home, individuals are asked to walk for at least 20 minutes daily over the one-year study period."

We assessed medial knee pain for a second time during this visit. A member of the study team palpated the medial, patellofemoral, and lateral regions of the knee, then evaluated pain bilaterally in each compartment of the knee on the numeric rating scale. In the knee with greater medial pain, if the medial pain was greater than 3, and medial pain was greater than patellofemoral or lateral pain, the individual was taken to the radiology clinic for an x-ray.

We took five bilateral x-ray views: weight-bearing leg-length, weight-bearing anterior-posterior view, weight-bearing notch view, weight-bearing lateral view, and sunrise view. These x-rays were then graded by a radiologist with more than 20 years of experience (GEG), who provided a Kellgren-Lawrence score. Study staff measured the mechanical limb alignment from the leg-length view using ImageJ (v1.50a, National Institutes of Health and the Laboratory for Optical and Computational Instrumentation, Madison, WI), using the center of the femoral head, the midpoint of the tibial plateau, and the midpoint of the medial and lateral malleoli.

Treadmill familiarization visit
Individuals whose pain and x-ray readings met inclusion criteria were invited to the Stanford Human Performance Laboratory to acclimate to walking with biofeedback on the split-belt, force-instrumented treadmill (Bertec Corporation, Columbus, OH, USA). Prior to treadmill walking, we assessed medial knee pain for a third time. If pain continued to meet inclusion criteria, they proceeded with treadmill walking. We first assessed self-selected walking speed by averaging overground walking speed over a 20m walkway using timing gates (Fusion Sport Inc., Brisbane, Australia) placed 6.1m apart, starting 10m into the walkway. Next, if individuals had not walked on a treadmill over the past year or were not comfortable walking on a treadmill without using the hand rails, they practiced walking at their self-selected speed on a standard single-belt treadmill (Woodway Inc., Waukesha, Wisconsin) until comfortable walking without holding onto the hand rails (minimum of five minutes).

Individuals then walked on the split-belt treadmill with motion capture and biofeedback. We placed a limited set of motion capture markers bilaterally on the shanks and feet, affixed the vibrotactile motors using a neoprene wrap, and confirmed that individuals could feel the vibration on either side of their shank. Participants then walked on the treadmill under the following conditions until they felt comfortable (minimum of 10 minutes per condition): natural walking without feedback, 10° toe-in (relative to natural foot progression angle) with feedback, and 10° toe-out with feedback. Participants were given an Omron HJ-323U pedometer (Omron Corporation, Kyoto, Japan) to carry with them for at least nine days prior to the next visit. They were also given a walking log to record their total daily walking time (for walking bouts >1min).

Week 0 visit
At least nine days later, participants completed the foot progression angle personalization (i.e., week 0) visit. We collected the pedometer, walking log, and assessed medial knee pain. This medial knee pain assessment was the fourth assessment taken over the span of five or more weeks. This pain-assessment run-in period was designed to reduce the effects of regression to the mean, thus, this week 0 assessment was used as the baseline value for the primary outcome of change in pain. Individuals then completed the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) survey on a computer. We placed retroreflective markers on the torso, pelvis, and lower extremities.[6] After warming up on the treadmill for five minutes, participants completed a two-minute natural walking trial. They then practiced walking with 5° and 10° toe-in and toe-out for at least one minute or until they felt comfortable. Finally, the participants walked for two minutes or until they achieved at least 30 successful steps (within 2·5° of the target foot progression angle) at each of the four foot progression angle modifications in a random order.

We limited the intervention options to 5° and 10° of toe-in and toe-out to prioritize effective load reduction and high adherence. Larger foot progression angle modifications tend to be less comfortable, potentially reducing adherence. Previous studies have used a range of 10° toe-in to 30° toe-out,[7,8] but we limited the toe-out range to 10° as it was both comfortable and sufficient to reduce the late-stance knee adduction moment peak.[9] We chose four discrete foot progression angle bins, separated by 5°, because greater precision is unlikely to be maintained outside the lab (studies have shown errors of 2° after 6 weeks of retraining[10]).

Following this visit, the foot progression angle, early-stance knee adduction moment peak, and late-stance knee adduction moment peak were averaged over the final 20 successful steps (i.e., within 2·5° of the target angle) of each trial. Each participant's larger knee adduction moment peak was identified from the natural walking trial, and the foot progression angle modification that maximally reduced this peak was identified. For individuals whose early and late-stance knee adduction moment peaks were within 5% of one another, the foot progression angle that maximally reduced one peak without increasing

the other was selected. Only individuals who were able to reduce their knee adduction moment peak by at least 5% remained eligible.[11]

We targeted the larger knee adduction moment peak due to the large amount of evidence relating the early-stance, late-stance, and larger knee adduction moment peak to radiographic severity, radiographic progression, and symptom severity.[12–14] Other studies have highlighted the importance of other scalar reductions of the knee adduction moment curve, like the impulse,[15] but we chose to target the peak due to the large number of studies relating it to clinically relevant outcomes. There is not clear evidence supporting greater importance of either the early- or the late-stance knee adduction moment peak, so we chose to target the larger of the two peaks (i.e., the overall peak during the stance phase).

MRI visit
Participants who remained eligible after the week 0 visit received an MRI, detailed in the *Magnetic Resonance Imaging* section below.

Week 1–6 visits
All eligibility criteria were assessed prior to the week 1 visit, thus individuals who completed the week 1 visit were included in the study and the intent-to-treat analysis. Immediately prior to the week 1 visit, a member of the study team randomized the eligible participant by unhiding a row on a spreadsheet (see Methods: Randomization and Masking in the manuscript). Individuals were not told at any time during the study that there was an "intervention" or a "sham" group but were instead told that the study was evaluating the relative efficacy of two personalized walking training interventions. Study staff described the group allocation to individuals by reading one of the following group-specific intervention descriptions:

> *Intervention group*: "From the data we collected last week, we found a change in foot progression angle that can reduce loading in your knee. For the duration of the study, we will be teaching you to walk very consistently with your personalized foot progression angle, which is [insert personalized target foot progression angle modification (e.g., 10° toe-in)]. For the next six weeks, you will visit the lab weekly and receive biofeedback for between 12 and 24 minutes. The goal of these training visits is for you to learn to walk consistently with your personalized foot progression angle so it becomes a natural part of how you walk at all times. When you are not in the lab, we ask that you practice walking consistently with this angle for a minimum of 20 minutes per day; once you are comfortable with it, the goal is to walk this way any time that you walk."
>
> *Sham group*: "From the data we collected last week, we found that there is a large amount of variability in your foot progression angle when you walk, and these aberrant steps can have higher loads in your knee. For the duration of the study, we will be teaching you to walk very consistently with your personalized foot progression angle, which is the average of all the steps you took without feedback during the last visit. The goal is to reduce how often you take aberrant steps. For the next six weeks, you will visit the lab weekly and receive biofeedback for between 12 and 24 minutes. The goal of these training visits is for you to learn to walk consistently with your personalized foot progression angle so it becomes a natural part of how you walk at all times. When you are not in the lab, we ask that you practice walking consistently with this angle for a minimum of 20 minutes per day; once you are comfortable with it, the goal is to walk this way any time that you walk."

We used the term 'personalized foot progression angle' to describe the target for biofeedback to all study participants. In this article, we refer to this target angle as the 'target foot progression angle,' and we refer to a 'personalized foot progression angle modification' as the toe-in or toe-out change in foot progression angle assigned to the intervention group.
At the beginning of the week 2–6 gait training visits, participants performed a two-minute pre-training evaluation trial without feedback. During all training visits (weeks 1–6), they then completed four blocks of biofeedback (12–24 minutes per visit) following a faded feedback scheme (Figure S1).[16] Each participant had a target foot progression angle; during biofeedback trials, they received a vibration if a step was more than 2° away from this target angle. For example, an individual in the sham group who walked with 3° toe-out on average during the week 0 natural walking trial (i.e., target absolute angle = 3° toe-out) would receive a vibration on their lateral shank for a step with less than 1° toe-out (i.e., "toe-out more next step"), a vibration on the medial shank for a step with more than 5° toe-out (i.e., "toe-in more next step"), and no vibration for a step with 1–5° toe-out (i.e., "correct foot angle"). Similarly, an individual in the intervention group who walked with 3° toe-out naturally (absolute angle) and was trained to walk with 10° toe-in relative to that angle (i.e., target absolute angle = 7° toe-in) would receive a medial-shank vibration for a step with less than 5° absolute toe-in (8° relative toe-in; i.e., "toe-in more next step"), a lateral-shank vibration for a step with more than 9° absolute toe-in (12° relative toe-in; i.e., "toe-out more next step"), and no vibration for a step with 5–9° absolute toe-in (8–12° relative toe-in; i.e., "correct foot

angle"). After training, participants completed a one-minute post-training evaluation trial without feedback. Between visits, participants completed daily walking logs to record daily walking time (sum of walking bouts >1min in duration) and the percentage of time walking with their target foot progression angle. At the end of each visit, study staff reviewed the walking logs with participants and encouraged them to meet their walking goals (walk for a total of at least 20 minutes per day and walk with the foot angle goal 100% of walking time). Since the ability to walk for 25 minutes was an inclusion criterion, the 20-minutes-per-day walking goal was selected as a sub-maximal amount of daily walking.

At the beginning of the week 6 visit, we assessed medial knee pain, and participants completed the WOMAC survey. At the end of this visit, participants were instructed to continue with their walking goals (walk for at least 20 minutes per day and walk with the foot angle goal 100% of walking time) and were sent home with walking logs to complete every day until the week 10 follow-up visit. Participants were compensated $100 (USD) for their time and parking costs at the end of this visit.

Week 10, Month 6, and Month 9 follow-up visits
At the beginning of each follow-up visit, following assessment of medial knee pain, participants performed a two-minute pre-training walking evaluation without feedback. Then, they performed three six-minute trials with biofeedback to remind them of their target foot progression angle followed by a one-minute post-training evaluation without feedback. At the end of each visit, study staff reviewed the walking logs with participants and encouraged them to meet their walking goals. Participants were compensated $100 at the end of the month 6 visit.

Year 1 visit
Prior to visiting the gait laboratory during the year 1 visit, individuals received an MRI. Upon arrival to the gait laboratory, we then evaluated their medial knee pain, and collected their pedometer, which they were instructed to carry for at least nine days prior to the visit. Participants then estimated the percentage of time that they walked with their target foot progression angle (i.e., compliance) for the week preceding the year 1 visit. Participants were compensated $150 at the end of this visit, for a total compensation of $350 over the study duration.

Study personnel
Four employees of the Palo Alto Veterans Affairs Hospital were trained to recruit participants, perform screening calls, and enroll them in the study during the x-ray visit. One of these employees, along with four other Stanford University affiliates, performed the gait retraining visits at the Stanford Human Performance Lab; these five individuals had at least a bachelor's degree in engineering and were proficient in conducting motion capture experiments. One of three Stanford affiliates—who did not conduct participant recruitment, screening, or enrollment—performed randomization prior to the week 1 visit. All staff were trained in the language used to describe the gait retraining to help maintain the participant blinding. All staff used the same scripts (reported above) for the description of the study, description of group allocation, and collection of self-reported outcomes. The retraining was an individual intervention, so study participants were never in the laboratory at the same time as another participant.

Use of co-interventions
Individuals were not allowed to use co-interventions throughout the duration of the study (e.g., physical therapy, intra-articular injections, knee braces, or wedged insoles). They were also not allowed to regularly use oral or topical pain medications. Individuals who regularly used pain medications were asked to discontinue use for one month (non-steroidal anti-inflammatory drugs) or two months (narcotics) prior to their scheduled x-ray visit and be willing to discontinue their use for the duration of the study. We did allow the non-regular use of oral non-steroidal anti-inflammatory drugs between the week 10 visit and the month preceding the year 1 visit. Individuals recorded their pain medication use on their walking activity logs, so we could confirm that they were not using the medications regularly (i.e., daily) during the follow-up period and that they discontinued use the month prior to the year 1 visit. No individuals who completed the year 1 visit used pain medications during the month preceding the visit.

Figure S1: **A faded feedback scheme for gait retraining visits.** Each gait retraining visit comprised four bouts of training, with total training time increasing from 12 to 24 minutes. During the latter three retraining sessions, feedback was only provided during the beginning of each feedback trial to enhance retention.[7,16]

Gait Analysis

During all 12 visits to the gait laboratory, individuals walked on a force-instrumented treadmill in an 11-camera optical motion capture volume (Motion Analysis Corp., Santa Rosa, CA, USA). Forces and marker positions were collected at 2000Hz and 100Hz, respectively, and data were low-pass filtered at 15 Hz (4^{th} order, zero-lag Butterworth). MATLAB R2015b (MathWorks, Inc., Natick, MA, USA) was used to compute the knee adduction moment and foot progression angle as well as to deliver real-time vibrotactile feedback through two C2 vibrotactile motors (Engineering Acoustics, Inc., Casselberry, FL, USA) affixed to the proximal tibia as described in Uhlrich et al.[6,9]

Magnetic Resonance Imaging

We utilized quantitative MRI to measure cartilage quality, to understand whether unloading of the medial compartment through modifications of the foot progression angle has an effect on cartilage microstructure. Femoral cartilage microstructure was evaluated at week 0 and at year 1 using quantitative MRI ($T_{1\rho}$ and T_2 relaxation times). All scans were performed at 3T (DISCOVERY MR750, General Electric Company, Boston, MA, USA) using a 16-channel phased-array flexible coil. Relaxation parameters in femoral cartilage have been reported to decrease immediately following acute loading,[17] and to normalize within 20 minutes even after intense activities such as running.[18] All participants arrived at the scanner at least 30 minutes before the scan, thus ensuring no short-term effect of loading history on quantitative parameters. All participants were placed in the scanner with their most affected knee in full extension and immobilized using a custom-built foot holder to ensure consistent positioning across participants. T_2 relaxation time data were acquired using a 3D quantitative Double Echo in Steady State (qDESS) sequence[19,20] (TR=24·96 ms, TE_1/TE_2=7·54/42·38 ms, FA=30°, FOV=160x160x120 mm^3, voxel size=0·3125x0·3125x1·5 mm^3, scan time=5 min 32 s). $T_{1\rho}$ relaxation time data were acquired using a magnetization-prepared pseudo-steady-state 3D Fast Spin Echo sequence[21] (Spin Lock Frequency=500 Hz, TR/TE=1292/16 ms, flip angle=90°, FOV=160x160x120 mm^3, voxel size=0·5x0·625x3 mm^3, Spin Lock Time = 1, 10, 30, 60 ms, total scan time=5 min 12 s). T_2 relaxation times were calculated using signal models from the two qDESS echoes[22] and $T_{1\rho}$ relaxation times were calculated pixelwise using a mono-exponential decay model. The qDESS image acquired at the shortest echo time at week 0 was chosen as reference. All year-1 images were non-rigidly registered to the first echo of the qDESS baseline scan, and the transform applied to the corresponding parameter image ($T_{1\rho}$ and T_2). The reference scan was also utilized to manually segment the weightbearing regions of the medial and lateral condyles of the femoral cartilage. Weight-bearing areas were manually determined based on two coronal planes drawn on the most anterior and posterior aspects of the menisci, perpendicular to the cartilage surface. This segmentation was subsequently applied to all scans. The voxel-wise difference between follow-up and baseline scans was calculated and the mean difference in $T_{1\rho}$ and T_2 ($\Delta T_{1\rho}$ and ΔT_2) values were extracted. A denoising filter (three-dimensional median filter with radius=1) was applied to the difference maps to eliminate noise and spurious peaks, while preserving larger clusters of longitudinal changes. Image processing was performed using QMRITools,[23] and non-rigid registrations were implemented using Elastix.[24]

Sensitivity Analyses

We conducted a sensitivity analysis to evaluate the sensitivity of our primary outcomes to the method of imputation. The original study plan was to conduct intent-to-treat analyses using all participants who were enrolled and randomized in the study. Seven participants were missing gait analysis data (knee adduction moment primary outcome) at the primary endpoint (year 1) due to the COVID-19 institutional shutdown. These data were assumed to be missing completely at random because the missingness is not associated with unobserved measures.[25]

First, we examined differences in baseline characteristics between participants with complete data and incomplete data (Table S2) using t-tests for continuous variables and chi-square tests for categorical variables. There were no observed differences by missing data. The complete dataset including imputed data can be found at https://simtk.org/projects/gait_retraining.

Next, we compared the results of the intent-to-treat analysis of all 68 randomized participants with the intent-to-treat analysis of the 61 (90%) participants who completed the trial prior to the COVID-19 institutional shutdown (Table S3). Results did not differ between the two analyses. We also compared these results with the per-protocol analysis of the 56 (82%) of 68 participants with complete NRS pain data and the 49 (72%) of 68 participants with complete knee adduction moment data. Per-protocol results were consistent with both intent-to-treat analyses. Therefore, we retained our original analysis plan for the manuscript and report the intent-to-treat analyses using all 68 participants who were randomized.

Table S2: Participant baseline characteristics and outcome measures for individuals with complete data for every outcome and time point and incomplete data.

	Complete Cases		Incomplete Cases		
	Intervention (n=14, 41% of 34)	Sham (n=17, 50% of 34)	Intervention (n=20, 59% of 34)	Sham (n=17, 50% of 34)	*P*-value
Age	65·7	65·5	63·4	63·6	·26
KL[†]	2·5	2·1	2·0	2·1	·19
BMI	25·2	28·5	25·7	26·3	·26
Proportion female (%)	57	65	65	53	·88
Alignment (°)	-4·8	-3·8	-2·9	-4·2	·41
NRS medial knee pain[‡]	4·6	3·6	4·1	4·4	·56
Knee adduction moment peak (%BW*ht)[§]	3·67	3·26	2·95	3·33	·21
$T_{1\rho}$ medial (ms)	62·06	57·46	59·03	60·66	·92
T_2 medial (ms)	37·38	38·56	36·78	37·66	·34
$T_{1\rho}$ lateral (ms)	54·64	54·51	57·83	56·46	·14
T_2 lateral (ms)	37·08	38·49	36·12	36·21	·07
WOMAC pain[¶]	69·3	72·1	71·8	70·3	·92
WOMAC function[¶]	75·1	75·5	76·2	70·7	·64
Daily steps	7390	6345	5570	6210	·19

To examine mean differences between complete and incomplete cases, t-tests were used for continuous variables and chi-square tests for categorical variables. All values are reported for the week 0 time point. Note that 31 complete cases had complete data for all listed variables at all time points, which is less than the 49–56 individuals included in the per-protocol analysis, who had complete data for primary and secondary outcomes at week 0 and year 1.

[†]The Kellgren and Lawrence system for classifying radiographic osteoarthritis severity ranges from 0 to 4, with 0 indicating no radiographic features of osteoarthritis.

[‡]The numeric rating scale (NRS) is a 0–10 scale assessing typical pain in the medial compartment over the preceding week with 0 representing no pain and 10 representing the worst imaginable pain.

[§]The knee adduction moment peak when individuals walked at their natural foot progression angle normalized to bodyweight (BW) and height (ht).

[¶]Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scales range from 0–100 with higher scores indicating higher function or less pain.

Table S3: Sensitivity of primary outcomes to statistical treatment of missing data.

	Intervention Mean (SD)	**Sham** Mean (SD)	**Mean difference** Mean (95% CI)	***P*-value**
Originally planned multiple imputation for missing data (n=68 [100%])				
NRS medial pain*	-2·5 (2·2)	-1·3 (2·3)	-1·2 (-1·9, -0·5)	**·0013**
Knee adduction moment peak†	-0·17 (0·47)	0·08 (0·33)	-0·26 (-0·39, -0·13)	**·0001**
Multiple imputation for missing data, excluding individuals with COVID shutdown–related missing data (n=61 [90% of 68] analyzed)				
NRS medial pain*	-2·5 (2·3)	-1·1 (2·2)	-1·5 (-2·2, -0·7)	**·0001**
Knee adduction moment peak†	-0·18 (0·47)	0·11 (0·31)	-0·29 (-0·42, -0·16)	**<·0001**
Per-Protocol (n=49–56 [72–82% of 68] analyzed)				
NRS medial pain* (n=56, 82% of 68)	-2·7 (1·2)	-1·4 (1·7)	-1·3 (-2·1, -0·5)	**·0019**
Knee adduction moment peak† (n=49, 72% of 68)	-0·19 (0·45)	0·11 (0·26)	-0·30 (-0·52, -0·09)	**·0071**

*The numeric rating scale (NRS) is a 0–10 scale assessing typical pain in the medial compartment over the preceding week with 0 representing no pain and 10 representing the worst imaginable pain. A one-point change is considered clinically meaningful.[26]

†The knee adduction moment expressed as a percentage of bodyweight times height. Lower values indicate less medial joint loading. No clinically meaningful change has been established; however, reductions of 5% have elicited improvements in pain.[27]

Exploratory Outcomes

We evaluated Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain, WOMAC function, foot progression angle error, and daily steps at the week 0 (Table S4) and year 1 visits. Changes between week 0 and year 1 in these variables, along with self-reported compliance to the intervention at the year 1 visit, were considered exploratory outcomes. Between-group differences were compared using linear regression and per-protocol analysis (Table S5).

WOMAC
The Knee Injury and Osteoarthritis Outcome Score (KOOS) survey was completed online at week 0 and year 1. The WOMAC pain and function subscores were calculated from the KOOS (http://www.koos.nu/). The scores were transformed to a scale from 0 to 100. Subscores of 100 indicate no pain and unimpaired function.

Foot progression angle error
We computed the foot progression angle error at year 1 as the absolute value of the relative foot progression angle (relative angle = $\text{angle}_{\text{year1}}$ - $\text{angle}_{\text{natural,week0}}$) minus the absolute value of the target foot progression angle; thus, for the intervention group, positive foot progression angle error values are in the direction of the target foot progression angle from the natural foot progression angle (i.e., too large of a modification).

Compliance
Participants estimated the percentage time walking consistently with their target foot progression angle (i.e., compliance) for the week preceding the year 1 visit.

Daily steps
Participants carried an Omron HJ-323U pedometer (Omron Corporation, Kyoto, Japan) for nine days prior to the week 0 and year 1 visits. After excluding the first and last day of registered steps, to mitigate for partial-day wear, daily steps were averaged.

Results: exploratory outcomes
Participants in the intervention group reported that, when walking outside of lab visits, they walked with their target foot progression angle 29% (95% confidence interval: 12%, 46%) more than those in the sham group (Table S5). There were no other between-group differences with a 95% confidence interval that crossed 0.

Table S4: Baseline (week 0) values for exploratory outcomes.

	Intervention group (n=34)	Sham group (n=34)
WOMAC pain*	70·7 (12·9)	71·2 (11·2)
WOMAC function*	75·7 (14·2)	73·2 (13·1)
Daily steps	6343 (2678)	6280 (3073)
Walking speed (m/s)	1·19 (0·14)	1·17 (0·15)

Mean (standard deviation).

*WOMAC scales range from 0 to 100 with higher scores indicating higher function or less pain.

Table S5: Between-group comparison of changes in exploratory outcomes at year 1.

	Intervention group (SD)	Sham group (SD)	Mean difference Mean (95% CI; n)
Δ WOMAC pain*	14·8 (15·3)	8·0 (16·8)	6·8 (-1·0, 14·7; n=53)
Δ WOMAC function*	9·7 (13·1)	6·0 (16·0)	3·7 (-3·4, 10·9; n=53)
Foot progression angle error (°)†	0·3 (2·7)	0·3 (2·5)	0·0 (-1·3, 1·2; n=49)
Compliance (%)‡	74 (32)	45 (37)	**29 (12, 46; n=48)**
Δ Daily steps§	-399 (2863)	-58 (2577)	-341 (-1670, 989; n=44)

The mean and standard deviation (SD) of exploratory outcomes at year 1 and changes (Δ) in outcomes from week 0 to year 1, in addition to mean group difference and 95% confidence interval (CI) estimates from linear regression models. The number of participants with complete data for each outcome is noted. (bold: 95% CI does not cross 0)

*WOMAC scales range from 0 to 100 with higher scores indicating higher function or less pain. Δ indicates the change from week 0 to year 1.

†The error in the average foot progression angle at year 1 compared to the angle that was targeted for training. Positive values are a greater change in foot progression angle from the week 0 natural walking value than the target angle.

‡The percentage of walking time that participants reported achieving their assigned foot progression angle over the week preceding the year 1 visit ranging from 0–100%.

Outcome Values

The values of primary and exploratory outcomes at the week 0 and year 1 time points are shown in Table S6.

Table S6: Outcome values at week 0 and year 1.

	Intervention		Sham	
	Week 0	**Year 1**	**Week 0**	**Year 1**
Primary Outcomes				
NRS medial pain[*] (n=68)	4·3 (1·3)	1·8 (2·2)	4·0 (1·2)	2·7 (2·0)
Knee adduction moment peak[†] (n=68)	3·25 (1·05)	3·07 (1·04)	3·30 (1·05)	3·38 (1·04)
Exploratory Outcomes				
WOMAC pain[¶] (n=53)	70·0 (13·9)	84·81 (10·2)	71·11 (11·6)	79·07 (13·9)
WOMAC function[¶] (n=53)	76·3 (14·3)	86·03 (11·9)	73·15 (12·9)	79·14 (15·4)
Daily steps (n=44)	6915 (3101)	6516 (2839)	6831 (3303)	6773 (3218)

Mean (standard deviation). For primary outcomes, data from all 68 randomized participants is included, with missing data at year 1 imputed. For exploratory outcomes, only participants with complete data for the outcome are reported. Outcomes for which values were not computed at both time points (e.g., secondary MRI outcomes were an averaged voxel-by-voxel change over time) are not included.

[*]The numeric rating scale (NRS) is a 0–10 scale assessing typical pain in the medial compartment over the preceding week with 0 representing no pain and 10 representing the worst imaginable pain. A one-point change is considered clinically meaningful.[26]

[†]The knee adduction moment expressed as a percentage of bodyweight times height. Lower values indicate less medial joint loading. No clinically meaningful change has been established; however, reductions of 5% have elicited improvements in pain.[27] The knee adduction moment peak during natural walking is reported for both groups at week 0.

[¶]Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scales range from 0–100 with higher scores indicating higher function or less pain.

Exploratory Biomechanical Analysis

Knee adduction moment curves

The knee adduction moment curves at baseline, week 6, and year 1 for both groups are shown in Figure S2. Statistical analysis of changes in the peak knee adduction moment are shown in Fig. 2 of the main article.

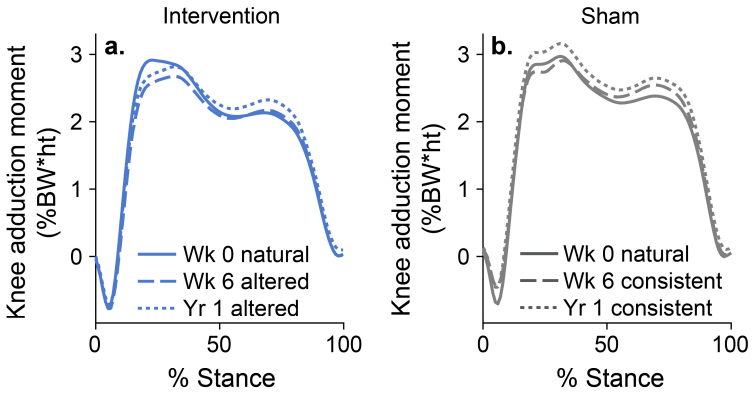


Figure S2: Changes in the knee adduction moment. Knee adduction moment curves, expressed as a percentage of bodyweight (BW) times height (ht) are shown for the 49 (72%) of 68 individuals who underwent gait analysis at year 1 (**a**, **b**). Larger values indicate greater loading in the medial compartment of the knee. Solid lines denote the average knee adduction moment during natural walking at week 0, and dashed lines indicate the knee adduction moment while participants aimed to walk at the target foot progression angle without biofeedback (altered foot progression angle for the intervention group and consistent angle for sham group) at week 6 and year 1.

Secondary kinematic and kinetic changes

It is important to consider the secondary kinematic and kinetic effects of the foot progression angle intervention. These secondary changes can cause gait modifications that reduce the knee adduction moment to not reduce medial compartment contact force[28] and could have deleterious effects on other joints. We previously showed that changes in foot progression angle do not increase hip joint moments on average, suggesting that for most individuals, the modifications do not increase hip contact forces.[29] Here we investigate the secondary changes in kinematics and knee joint kinetics at the four different foot progression angle modifications (Table S7) and over the duration of the trial (Table S8).

In Table S7, we use data from the week 0 visit, where all 68 (100%) individuals walked with the four progression angle modifications prior to randomization. We evaluate the peak knee adduction, flexion, and extension moments; increases in the magnitude of these moments can increase medial compartment contact force.[28,30] Importantly, we report the early- and late-stance peaks of the knee adduction moment (first and second peaks, respectively); elsewhere in the manuscript, we report on the knee adduction moment peak, which we define as the larger of the peaks during natural walking. We also evaluate kinematic parameters that can affect the knee adduction moment. All moments are expressed as external moments; methods for computing these kinematic and kinetic variables have been described previously.[6,9] In Table S8, we show how these biomechanical variables changed over the course of the trial for the 49 individuals who completed the trial. Using linear regression, we compute 95% confidence intervals around changes over time and across interventions, compared to natural walking at week 0. These analyses are exploratory, so we do not correct for multiple comparisons or present *P*-values. The confidence intervals should therefore be interpreted with caution and seen as hypothesis-generating.

In alignment with previous work, we found that a toe-in gait modification primarily reduced the first peak of the knee adduction moment while toe-out primarily reduced the second peak[31,32] (Table S7). Ninety-one percent (62 of 68) of individuals had a larger first peak knee adduction moment during natural walking. The effectiveness of a toe-in gait modification at reducing this peak in part explains why this modification was selected for 82% (28 of 34) of the intervention group. We have previously described the effects of toe-in and toe-out gait on the larger knee adduction moment peak, the importance of personalization, and the kinematic strategies that make the modifications more effective.[6]

The external knee extension moment peak increased when the intervention group walked with their target foot progression angle at week 0 (Table S8). This moment increased for all foot progression angle modifications (Table S7). The confidence intervals for changes in knee flexion and extension moments includes 0 at both week 6 and year 1. This suggests that the initial increases observed at week 0 attenuated as individuals became more comfortable walking on the treadmill with their target foot progression angle modification. Similarly, in the sham group, step width decreased at year 1 compared to baseline. The intervention group also trended in this direction, but the confidence interval includes 0 (Table S8). This suggests that individuals may have continued to become more comfortable walking on the split-belt treadmill over the duration of the study. As this treadmill acclimation effect applied similarly to both groups, it is unlikely to have impacted our primary outcome of between-group differences in the knee adduction moment; a between-group difference in the one-year change in knee adduction moment peak persisted at year 1, when individuals were likely the most comfortable walking on the treadmill.

Table S7: Kinematics and knee joint kinetics while walking with different foot angle modifications at week 0.

	Natural walking	10° toe-in	5° toe-in	5° toe-out	10° toe-out
Knee adduction moment peak 1 (%BW*ht)*	3·24 (1·02)	2·93 (0·97)	3·06 (0·98)	3·21 (1·03)	3·29 (1·05)
Change		**-0·31 (-0·37, -0·25)**	**-0·18 (-0·23, -0·13)**	-0·03 (-0·09, 0·03)	0·05 (-0·02, 0·12)
Knee adduction moment peak 2 (%BW*ht)*	2·43 (0·93)	2·41 (0·92)	2·37 (0·91)	2·24 (0·93)	2·16 (0·94)
Change		-0·01 (-0·06, 0·03)	**-0·06 (-0·10, -0·02)**	**-0·19 (-0·23, -0·15)**	**-0·27 (-0·33, -0·21)**
Knee flexion moment peak (%BW*ht)*	3·23 (1·23)	3·11 (1·43)	3·23 (1·36)	3·48 (1·35)	3·57 (1·39)
Change		-0·11 (-0·25, 0·03)	0·01 (-0·09, 0·11)	**0·25 (0·15, 0·35)**	**0·34 (0·22, 0·46)**
Knee extension moment peak (%BW*ht)*	-1·39 (0·94)	-1·21 (1·07)	-1·16 (1·02)	-1·03 (0·95)	-1·00 (0·88)
Change		**0·18 (0·07, 0·30)**	**0·23 (0·15, 0·32)**	**0·36 (0·27, 0·45)**	**0·39 (0·28, 0·49)**
Step width (cm)	19·1 (3·5)	20·0 (3·9)	19·6 (3·5)	21·0 (3·9)	22·9 (4·5)
Change		**0·9 (0·2, 1·5)**	0·4 (-0·1, 1·0)	**1·8 (1·3, 2·3)**	**3·8 (3·2, 4·4)**
Peak knee flexion angle (°)	8·7 (2·1)	9·0 (2·4)	8·9 (2·3)	8·6 (2·3)	8·5 (2·3)
Change		**0·3 (0·1, 0·5)**	**0·2 (0·0, 0·4)**	-0·1 (-0·3, 0·1)	**-0·2 (-0·4, -0·0)**
Peak knee adduction angle (°)	2·6 (4·7)	2·4 (4·5)	2·5 (4·5)	2·6 (4·6)	2·7 (4·7)
Change		**-0·2 (-0·3, -0·0)**	-0·1 (-0·3, 0·0)	0·0 (-0·1, 0·1)	0·0 (-0·1, 0·2)
Trunk sway angle (°)	2·1 (2·0)	1·4 (2·2)	1·7 (2·1)	2·6 (3·6)	3·0 (3·8)
Change		**-0·6 (-0·9, -0·4)**	**-0·4 (-0·6, -0·1)**	0·5 (-0·3, 1·2)	**0·9 (0·2, 1·6)**

Mean (standard deviation) and mean change (95% confidence interval). Changes for which the confidence interval does not cross 0 are bold. Data are from all 68 (100%) individuals during the week 0 visit where everyone walked with all foot progression angle modifications.

*External moments are expressed as a percentage of bodyweight (BW) times height (ht). The first (early-stance) and second (late-stance) peaks are reported here, which differs from the knee adduction moment peak (the larger peak during natural walking) which is reported elsewhere in the manuscript.

Table S8: Changes in kinematics and knee joint kinetics over the duration of the trial.

	Intervention (n=25, 74% of 34)				Sham (n=24, 71% of 34)		
	Week 0 natural angle	**Week 0 altered angle**	**Week 6**	**Year 1**	**Week 0**	**Week 6**	**Year 1**
Knee adduction moment peak 1 (%BW*ht)*	3·27 (0·92)	2·92 (0·94)	3·00 (1·00)	3·13 (0·99)	3·32 (1·16)	3·19 (1·00)	3·46 (1·12)
Change		**-0·36 (-0·43, -0·28)**	**-0·28 (-0·47, -0·08)**	-0·15 (-0·35, 0·06)		-0·13 (-0·27, 0·01)	0·14 (0·01, 0·26)
Knee adduction moment peak 2 (%BW*ht)*	2·39 (0·98)	2·31 (0·95)	2·35 (0·84)	2·53 (0·98)	2·60 (0·85)	2·70 (0·87)	2·83 (0·98)
Change		-0·08 (-0·17, 0·00)	-0·03 (-0·18, 0·11)	0·14 (-0·01, 0·29)		0·10 (-0·02, 0·22)	0·23 (0·23, 0·39)
Knee flexion moment peak (%BW*ht)*	3·36 (1·25)	3·28 (1·54)	3·22 (1·25)	3·11 (1·44)	3·24 (1·22)	2·90 (1·13)	2·88 (1·29)
Change		-0·08 (-0·34, 0·17)	-0·15 (-0·58, 0·29)	-0·26 (-0·66, 0·15)		-0·34 (-0·72, 0·05)	-0·36 (-0·80, 0·07)
Knee extension moment peak (%BW*ht)*	-1·24 (0·84)	-1·05 (0·84	-1·26 (1·04)	-1·37 (1·26)	-1·34 (0·93)	-1·26 (0·84)	-1·40 (1·04)
Change		**0·20 (0·08, 0·32)**	-0·01 (-0·35, 0·33)	-0·13 (-0·50, 0·25)		0·08 (-0·18, 0·34)	-0·05 (-0·34, 0·24)
Step width (cm)	18·4 (3·2)	19·2 (3·2)	18·4 (3·8)	17·4 (3·3)	19·3 (4·1)	18·5 (4·1)	17·8 (4·1)
Change		0·8 (-0·2, 1·9)	0·0 (-1·4, 1·4)	-1·0 (-2·3, 0·4)		-0·8 (-2·1, 0·5)	**-1·5 (-2·7, -0·3)**
Peak knee flexion angle (°)	8·8 (1·9)	8·8 (2·2)	8·8 (2·0)	8·8 (2·1)	9·0 (1·9)	8·5 (1·9)	8·3 (1·9)
Change		-0·0 (-0·4, 0·4)	-0·0 (-0·6, 0·6)	-0·0 (-0·8, 0·7)		-0·5 (-1·0, 0·1)	-0·7 (-1·4, 0·0)
Peak knee adduction angle (°)	2·6 (4·8)	2·5 (4·8)	3·5 (5·3)	4·0 (5·0)	3·0 (4·8)	3·1 (4·1)	3·3 (5·0)
Change		-0·1 (-0·4, 0·1)	0·9 (-0·5, 2·2)	1·4 (-0·0, 2·8)		0·2 (-0·7, 1·0)	0·3 (-0·9, 1·5)
Trunk sway angle (°)	2·2 (2·2)	1·7 (2·3)	1·5 (2·1)	2·2 (1·8)	2·3 (1·7)	2·6 (1·8)	2·5 (1·7)
Change		-0·5 (-1·1, 0·0)	**-0·7 (-1·3, -0·1)**	-0·4 (-1·0, 0·2)		0·3 (-0·2, 0·8)	0·2 (-0·5, 0·9)

Mean (standard deviation) and mean change (95% confidence interval). Data from the 49 (72%) of 68 individuals who completed every trial visit are included. Changes for which the confidence interval does not cross 0 are bold.

*External moments are expressed as a percentage of bodyweight (BW) times height (ht). The first (early-stance) and second (late-stance) peaks are reported here, which differs from the knee adduction moment peak (the larger peak during natural walking) which is reported elsewhere in the manuscript.

Foot progression angle performance over time

To assess learning, we evaluated foot progression angle error for the intervention group and foot progression angle variability (the standard deviation in foot progression angle) for the sham group during each visit for trials where biofeedback was not provided. During training and follow-up visits, participants completed walking trials before and after receiving biofeedback. During the pre-training trial, they were instructed to walk how they had been walking outside the lab during the previous week. During the post-training trial (after biofeedback), they were instructed to walk how they had just received feedback to walk. There was no pre-training trial at week 1, as there had not been any prior training to evaluate. Similarly, there was no post-training trial at year 1 because there was no biofeedback provided during this visit. Using linear regression, we compared performance during these non-feedback trials at week 6 and year 1, compared to baseline (week 2 for intervention, week 0 for sham). We also compared performance between the pre-training and post-training trials at week 6 and month 9 (the final visit that included both trials). These analyses are exploratory, so we did not correct for multiple comparisons or present *P*-values. The confidence intervals should therefore be interpreted with caution and seen as hypothesis-generating.

Foot progression angle performance improved, compared to baseline, in both groups after six weeks of training and at year 1 (Figure S3). In the intervention group, foot progression angle error during the pre-training walking trial decreased from week 2 to week 6 (-2·04° change; 95% confidence interval: -3·62, -0·45°). The error remained lower at year 1 compared to week 2 (-2·13° change; 95% confidence interval: -3·69°, -0·56°). Error during the post-training trial was lower than the pre-training trial at week 6 (-0·95° difference; 95% confidence interval: -1·66°, -0·23°) but not month 9 (-0·69° difference; 95% confidence interval: -1·77°, 0·39°). Error over time, grouped by target foot progression angle, is shown in Table S9. In the sham group, foot progression angle variability decreased (Figure S3) from the week 0 natural walking trial to the week 6 pre-training trial (-0·32° change; 95% confidence interval: -0·47°, -0·17°). The variability remained lower at year 1 compared to week 0 (-0·15° change; 95% confidence interval: -0·27°, -0·02°). Variability was not different between the pre-training and post-training trials at either week 6 (-0·01° difference; 95% confidence interval: -0·17°, 0·14°) or month 9 (-0·01° difference; 95% confidence interval: -0·15°, 0·12°).

The improvement in performance over the six weeks of training during the pre-training trial suggests that individuals in both groups learned their foot progression angle objective such that they were able to perform it without feedback, and likely were able to do so during out-of-lab walking. However, our in-laboratory assessments, walking logs, and self-reported compliance questions cannot conclusively determine out-of-laboratory behavior. It is possible that participants only walked with their target foot angle during laboratory evaluations. This is unlikely, given the between-group differences that we observed in both pain and MRI-based measures of cartilage health. Algorithms for estimating the foot progression angle from wearable sensor data, which were not available at the beginning of our study, could be used in future studies to study out-of-laboratory compliance over long durations.[33] The retained performance improvement at month 9 suggests that the six weeks of training was sufficient for medium-term retention without the need for continuous weekly biofeedback. Performance in both groups generally improved over the six weeks of training, and it is possible that further training could have yielded further improvements. However, the six weeks of feedback resulted in errors at year 1 of less than 1° in the intervention group; further performance improvement would likely only have a marginal impact on knee loading.

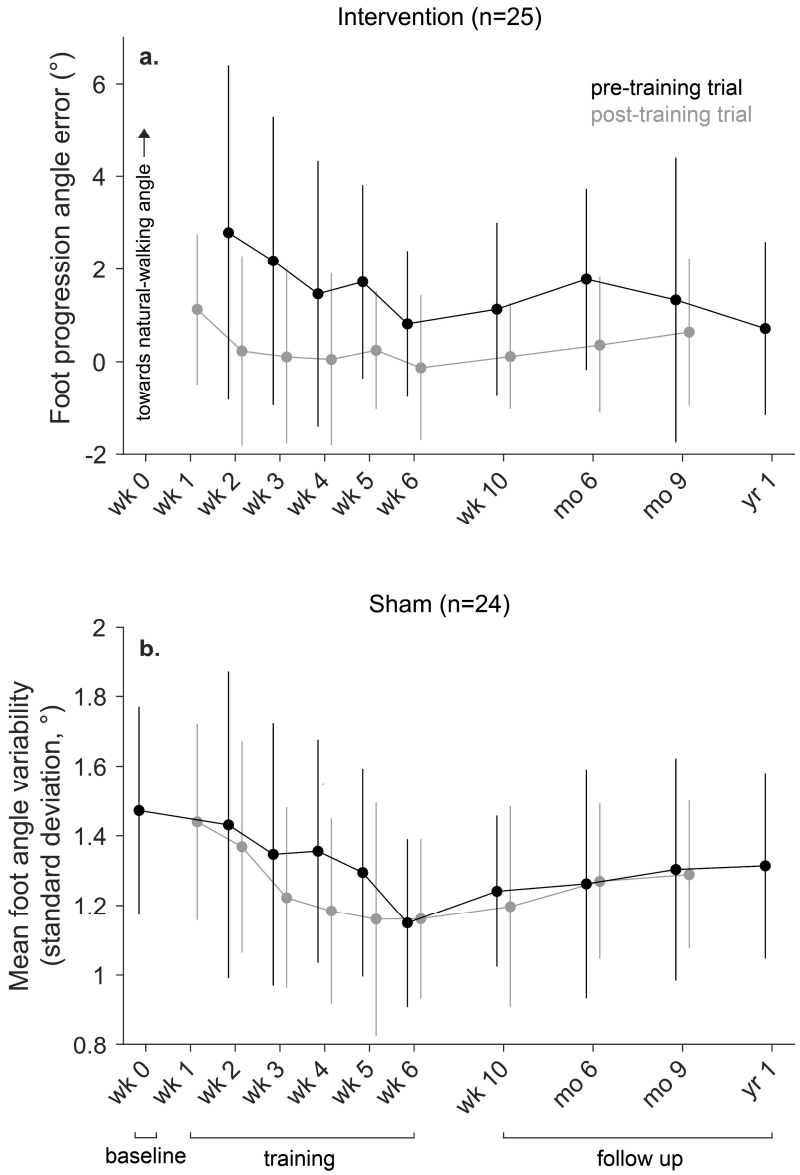


Figure S3: Foot progression angle performance across all trial visits for individuals who completed all trial visits (n=49, 72% of 68). The average and standard deviation of foot progression angle error for the intervention group **(a)**. At the beginning of each visit, individuals walked without biofeedback to evaluate retention (i.e., pre-training trial, black). After training with biofeedback, they walked again without biofeedback (i.e., post-training trial, gray). Since some individuals were taught to increase, and some to decrease, their foot progression angle, error is signed such that positive values indicate an error in the direction of the natural foot angle. The average and standard deviation of variability (standard deviation over a trial) in foot progression angle over each trial for the sham group **(b)**.

Table S9: Foot progression angle error grouped by target foot progression angle modification.

Target foot progression angle modification (°)	Week 2	Week 6	Year 1
10° toe-in (°, n=14)	3·8 (3·2)	0·9 (1·6)	0·9 (1·9)
5° toe-in (°, n=5)	2·0 (2·0)	-0·5 (0·6)	0·2 (1·9)
5° toe-out (°, n=1)	-4·5 (-)	0·3 (-)	-0·1 (-)
10° toe-out (°, n=5)	1·9 (3·8)	2·1 (0·8)	0·9 (1·8)

The mean and standard deviation of foot progression angle error during the pre-training trial for the individuals in the intervention group who completed all trial visits (n=25, 74% of 34). Error is signed such that positive values indicate an error in the direction of the natural foot angle.

Self-reported walking logs

Data from the daily walking logs for the weeks preceding the week 0, week 6, and year 1 visits are presented in Table S10. Using linear regression, we compute 95% confidence intervals around between-group differences in daily walking minutes and percentage of time walking with the personalized foot progression angle at each time point. These analyses are exploratory, so we do not correct for multiple comparisons or present *P*-values. The confidence intervals should therefore be interpreted with caution and seen as hypothesis-generating.

The average self-reported daily walking minutes across groups and time points was 48–67 minutes per day. The 95% confidence intervals for the between-group difference in walking minutes included 0 at all time points. The self-reported percentage of time walking at the personalized foot progression angle was 17% (95% CI: 3, 31) greater in the intervention group at week 6 and 27% (95% CI: 10, 44) greater at year 1. This aligns with the 29% (95% CI: 12, 46) greater self-reported intervention compliance in the intervention group (Table S5).

Table S10: Self-reported data from walking logs.

	Week 0			Week 6			Year 1		
	Intervention	**Sham**	**Difference**	**Intervention**	**Sham**	**Difference**	**Intervention**	**Sham**	**Difference**
Self-reported daily walking time (min)*	67 (46)	51 (40)	15 (-9, 40)	59 (63)	53 (36)	6 (-23, 35)	69 (47)	48 (32)	20 (-2, 43)
Self-reported intervention compliance (%)†				63 (25)	46 (23)	**17 (3, 31)**	68 (32)	41 (29)	**27 (10, 44)**

The mean and standard deviation of self-reported walking log data from the week preceding the in-laboratory visit. Data are from the individuals with complete walking log data at the assessed time points (n=50, 74% of 68). The between-group difference and 95% confidence interval is bold if the confidence interval excludes 0.

*Participants recorded the total number of walking minutes per day, only including walking bouts lasting longer than one minute.

†Participants recorded the percentage of their daily walking minutes that they were walking consistently with their target foot progression angle.

Interpretation of pain effect size

The IMMPACT recommendations for determining clinical importance of pain findings in clinical trials[34] recommend that clinical significance of pain results in trials be evaluated by comparing the proportion of individuals in each group who experience a clinically meaningful pain improvement. Thus, we used a responder analysis as our main assessment of the clinical significance of our NRS pain results. This responder analysis is discussed in the manuscript and demonstrates that the intervention group had a higher relative probability of experiencing a clinically important pain improvement than the sham group (relative risk ratio = 1·26; 95% CI: 1.04, 1.56).

Another approach to determining clinical importance in meta-analyses is to compare standardized mean differences (SMD) to SMD minimal clinically important difference (MCID) thresholds (Figure S4). The 0·53 (95%CI: 0·22, 0·84) SMD for our intervention would be considered a clinically significant according to a recent systematic review[35] since the lower confidence interval (0·22) exceeds the lowest definition of a clinically important difference (0·2). However, considering the range of MCID thresholds that have been proposed[35] (0·2–0·5), our SMD is greater than all MCID values in the range, but the confidence interval includes higher thresholds in the range. Thus, a more conservative interpretation using the higher MCID thresholds would be that the group effect was "possibly clinically significant." Notably, none of the common treatments shown in Figure S4 have confidence intervals that exclude the highest possible MCID threshold, despite many of them being commonly used in clinical practice and widely considered effective.[36] This uncertainty in MCID thresholds is one of the limitations of evaluating the clinical importance of a single clinical trial based on between-group differences and highlights why we chose to evaluate the clinical significance of the pain results in our study with a responder analysis, as recommended by IMMPACT.[34]

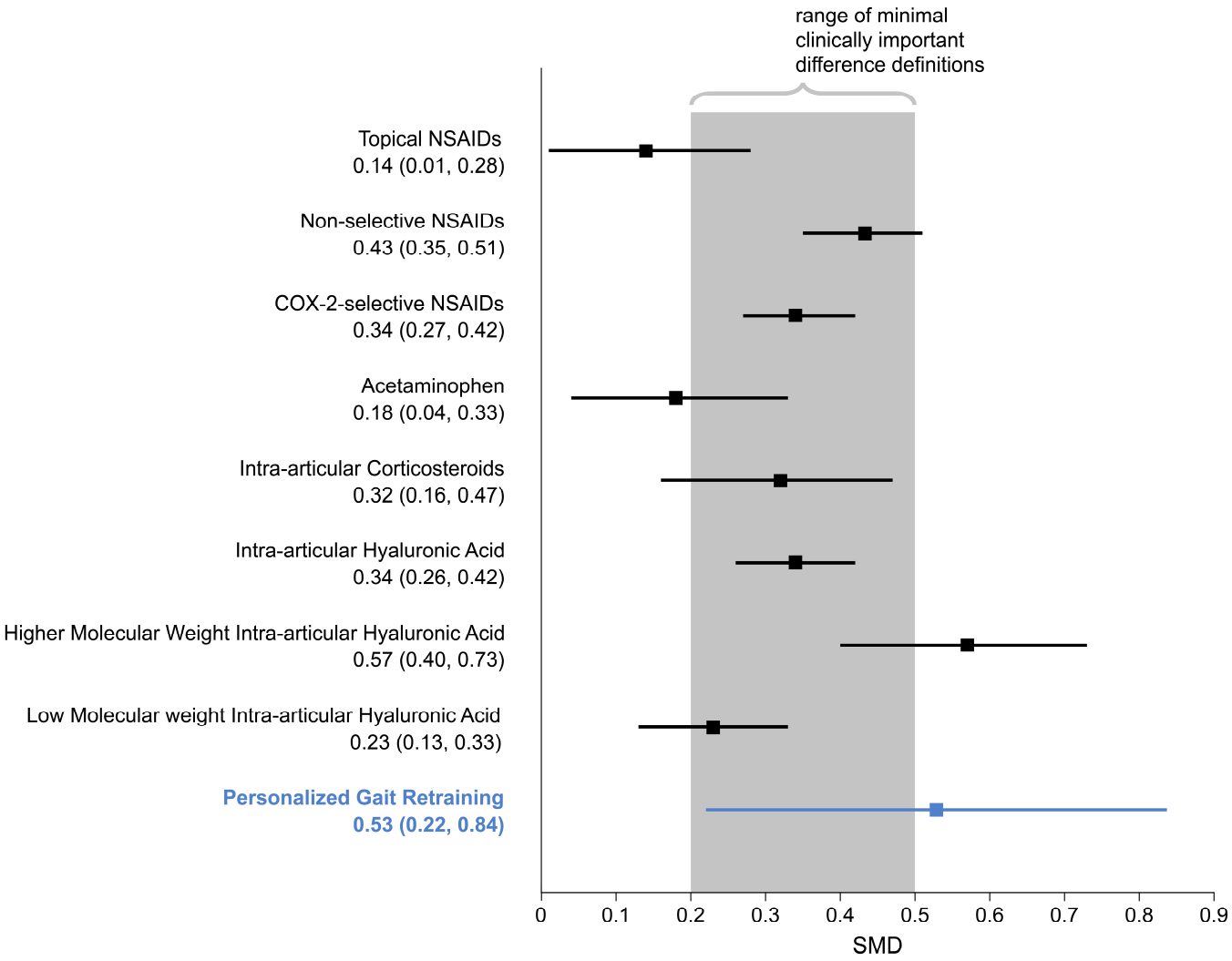


Figure S4: Standardized mean differences (SMD) and 95% confidence intervals of common non-surgical treatments for knee osteoarthritis. All data, excluding the results of our study (personalized gait retraining) are from a published systematic review.[35]

Primary outcomes disaggregated by sex

The primary outcome values, disaggregated by sex, are shown in Table S11. This is an exploratory analysis; the study was not powered to detect sex differences in the primary outcomes. There were three reported adverse events, two in the intervention and one in the sham group. All three of the participants who reported these events—an increase in medial or patellofemoral pain—were male.

Table S11: Primary outcomes disaggregated by sex from per-protocol analysis.

	Intervention Mean (SD)	**Sham** Mean (SD)	**Mean difference** Mean (95% CI)
NRS medial pain* (n=56, 82% of 68)			
Female (n=35, 62% of 56)	-2·8 (1·4)	-1·4 (1·5)	-1·5 (-2·5, -0·4)
Male (n=21, 38% of 56)	-2·4 (0·9)	-1·3 (2·0)	-1·1 (-2·6, 0·5)
Knee adduction moment peak† (n=49, 72% of 68)			
Female (n=34, 69% of 49)	-0·27 (0·41)	0·12 (0·27)	-0·39 (-0·64, -0·14)
Male (n=15, 31% of 49)	0·01 (0·48)	0·10 (0·26)	-0·08 (-0·53, 0·36)

*The numeric rating scale (NRS) is a 0–10 scale assessing typical pain in the medial compartment over the preceding week with 0 representing no pain and 10 representing the worst imaginable pain. A one-point change is considered clinically meaningful.[26]

†The knee adduction moment expressed as a percentage of bodyweight times height. Lower values indicate less medial joint loading. No clinically meaningful change has been established; however, reductions of 5% have elicited improvements in pain.[27]

Safety data

There were no severe adverse events in the trial. Three adverse events were observed, all including an increase in pain in either the medial or patellofemoral compartment. All three individuals dropped out of the trial prior to completion, but we collected their pain data and included them in the intent-to-treat analysis. The safety data is summarized in Table S12.

Table S12: Safety data.

	Intervention (n=34, 100%)	Sham (n=34, 100%)
Total adverse events	2 (6%)	1 (3%)
Increased medial knee pain	1 (3%)	1 (3%)
Increased patellofemoral pain	1 (3%)	0 (0%)

CONSORT Checklist

Note: Page numbers correspond to original submitted manuscript.

Section/Topic	Item No	Checklist item	Reported on page No.
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions	5–6
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	7
	2b	Specific objectives or hypotheses	8–9
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	10–14
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	NA
Participants	4a	Eligibility criteria for participants	9, Fig. 1
	4b	Settings and locations where the data were collected	9
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	11–13; Supp. Appendix 5–11
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	13
	6b	Any changes to trial outcomes after the trial commenced, with reasons	NA
Sample size	7a	How sample size was determined	13–14
	7b	When applicable, explanation of any interim analyses and stopping guidelines	14
Randomization:			
Sequence generation	8a	Method used to generate the random allocation sequence	10
	8b	Type of randomization; details of any restriction (such as blocking and block size)	10
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	10
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	10
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	10–11
	11b	If relevant, description of the similarity of interventions	11; Supp. Appendix 5–8
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	13–14
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	13; Supp. Appendix 12, 14, 31–32, 140–141
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome	15
	13b	For each group, losses and exclusions after randomization, together with reasons	15–16, Fig. 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	15
	14b	Why the trial ended or was stopped	15
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1
Numbers analyzed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	15–17
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	16–17, Table 2
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	Supp. Appendix 12–34
Harms	19	All important harms or unintended effects in each group	16, Supp. Appendix p33–34
Discussion			

Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	21–22
Generalizability	21	Generalizability (external validity, applicability) of the trial findings	18–22 , Table S1
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	18–22
Other information			
Registration	23	Registration number and name of trial registry	9
Protocol	24	Where the full trial protocol can be accessed, if available	9
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	15, 23–24

Changes in Trial Protocol from COVID-19 Pandemic (CONSERVE Checklist)

Study enrollment ended in July of 2019 due to the conclusion of funding. In March of 2020, Stanford University indefinitely suspended all in-person human subjects research that was not medically essential due to the COVID-19 pandemic. Since the pandemic could not have been foreseen, and there was no way to mitigate the loss of access to the laboratory, we considered the disruption to be due to *extenuating circumstances*.[37] At this time, seven participants had completed at least their 6-month visit but were still scheduled to return to the laboratory for either their nine-month (n=2) or one-year (n=5) visit.

The entire study team met to discuss how to continue the trial without the ability to bring participants into the laboratory. The length of the research shutdown was unknown at the time, so there was no option to modify the location and/or the timing of the remaining study visits. To mitigate the amount of data lost, we continued collecting self-report data over the phone (NRS pain, WOMAC, steps, and compliance) from patients at their normally scheduled visit intervals. During these phone calls, we encouraged participants to continue their walking practice, to the degree that was safe given current public health guidelines pertaining to the pandemic. There was no alternative way to collect the gait and MRI data, however, so these data were not collected for the remaining study visits. Thus, the two individuals who had not completed their nine-month visit prior to the shutdown did not complete in-lab gait retraining during this visit. This represents the only change in the delivered intervention. No trial data were analyzed as a part of the decision, and the entire study team planned, reviewed, and approved of the modifications.

Our pre-specified statistical analysis plan accounted for missing data by using an intent-to-treat analysis with multiple imputation for missing data. This missing data related to COVID-19 did not change this statistical analysis plan. However, to examine the impact of this missing data and the change in outcome collection methodology, we performed a sensitivity analysis to assess how the inclusion of the seven impacted participants impacted statistical outcomes. We performed multiple imputation on the 61 participants who completed the trial prior to the research shutdown and compared it to the n=68 intent-to-treat analysis that was pre-specified. There were no differences in the statistical significance of the primary outcomes (see *Sensitivity Analyses*). These modifications, particularly the inability to collect gait and MRI data on seven participants, were considered *important modifications* because they could have impacted the statistical power of the study.[37]

In summary, the COVID-19 shutdown impacted the delivery of the gait retraining intervention because two participants (one intervention, one sham) did not receive biofeedback at the nine-month visit. This was not possible to mitigate because the biofeedback occurred in the gait laboratory. The collection of outcomes was impacted, and we collected as many self-reported outcomes as possible to mitigate the loss of data. Participant flow was impacted, but we mitigated the modification by collecting as much data as possible remotely. Finally, we conducted an ancillary statistical analysis to determine the sensitivity of our results to the pandemic-related missing data as a mitigation strategy.

CONSERVE-CONSORT Extension					
Item	**Item Title**	**Description**			**Page No.**
I.	Extenuating Circumstances	Describe the circumstances and how they constitute extenuating circumstances.			Manuscript: 15, Supp. Appendix: 37
II.	Important Modifications	a. Describe how the modifications are important modifications.			Supp. Appendix: 37
		b. Describe the impacts and mitigating strategies, including their rationale and implications for the trial.			(see below)
		c. Provide a modification timeline.			Supp. Appendix: 37
III.	Responsible Parties	State who planned, reviewed and approved the modifications.			Supp. Appendix: 37
IV.	Interim data	If modifications were informed by trial data, describe how the interim data were used, including whether they were examined by study group, and whether the individuals reviewing the data were blinded to the treatment allocation.			N/A
CONSORT Number and Item		For each row, if important modifications occurred check "direct impact" and/or "mitigating strategy" and describe the changes in the trial manuscript or supplement. Check "no change" for items that are unaffected in the extenuating circumstance.			**Page No.**
		No Change	**Impact***	**Mitigating Strategy****	
1	Title and abstract	x			
2	Introduction	x			
3	Methods: Trial Design	x			
4	Methods: Participants	x			
5	Methods: Interventions		x		Supp. Appendix: 37
6	Methods: Outcomes		x	x	Supp. Appendix: 37
7	Methods: Sample Size	x			
8-10	Methods: Randomisation	x			
11	Methods: Blinding	x			
12	Methods: Statistical methods	x			
13	Results: Participant flow		x	x	Manuscript: Fig. 1, Supp. Appendix: 37
14	Results: Recruitment	x			
15	Results: Baseline data	x			
16	Results: Numbers analysed	x			

	Results: Outcomes and estimation	x			
18	Results: Ancillary analyses			x	Manuscript: 17, Supp. Appendix: 12, 14
19	Results: Harms	x			
20	Discussion: Limitations	x			
21	Discussion: Generalisability	x			
	Other information: Registration	x			
24	Other information: Protocol	x			
25	Other information: Funding	x			

*Aspects of the trial that are directly affected or changed by the extenuating circumstance and are not under the control of investigators, sponsor or funder.
**Aspects of the trial that are modified by the study investigators, sponsor or funder to respond to the extenuating circumstance or manage the direct impacts on the trial.

TIDieR Checklist

Note: Page numbers correspond to original submitted manuscript.

Item	Where located			Where located	
	Primary paper (page or appendix number)	Other (details)		Primary paper (page or appendix number)	Other (details)
Active intervention			**Placebo/sham intervention**		
1 Brief Name					
Provide the name or a phrase that describes the intervention	8, 11		Provide the name or a phrase that describes the placebo/sham intervention	8, 11	
2 Why					
Describe any rationale, theory, or goal of the elements essential to the intervention	7–8		Describe any rationale, theory, or goal of the elements essential to the placebo/sham intervention*	7–8	
3 What (materials)					
Describe any physical or informational materials used in the intervention, including those provided to participants or used in intervention delivery or in training of intervention providers. Provide information on where the materials can be accessed (such as online appendix, URL)	11–13 Supp. Appendix: 5–9		Describe any physical or informational materials used in the placebo/sham intervention, including those provided to participants or used in intervention delivery or in training of intervention providers. Provide information on where the materials can be accessed (such as an online appendix, URL)	11–13 Supp. Appendix: 5–9	
4 What (procedures)					
Describe each of the procedures, activities, and/or processes used in the intervention, including any enabling or support activities	11–13 Supp. Appendix: 5–9		Describe each of the procedures, activities, and/or processes used in the placebo/sham intervention, including any enabling or support activities	11–13 Supp. Appendix: 5–9	
5 Who provided					
For each category of intervention provider (such as psychologist, nursing assistant), describe their expertise, background, and any specific training given	Supp. Appendix: 8		For each category of placebo/sham intervention provider (such as psychologist, nursing assistant), describe their expertise, background, and any specific training given	Supp. Appendix: 8	
6 How					
Describe the modes of delivery (such as face to face or by some other mechanism, such as internet or telephone) of the intervention and whether it was provided individually or in a group	11–13 Supp. Appendix: 5–9		Describe the modes of delivery (such as face to face or by some other mechanism, such as internet or telephone) of the placebo/sham intervention and whether it was provided individually or in a group	11–13 Supp. Appendix: 5–9	
7 Where					
Describe the type(s) of location(s) where the intervention occurred, including any necessary infrastructure or relevant features	9		Describe the type(s) of locations(s) and settings where the placebo/sham intervention occurred, including any necessary infrastructure or relevant features	9	
8 When and how much					
Describe the number of times the intervention was delivered and over what period of time including the number of sessions, their schedule, and their duration, intensity, or dose	11–13 Supp. Appendix: 7–9		Describe the number of times the placebo/sham intervention was delivered and over what period of time including the number of sessions, their schedule, and their duration, intensity, or dose. If relevant, include the duration of the pre-, and post-randomisation consultations	11–13 Supp. Appendix: 7–9	
9 Tailoring					

If the intervention was planned to be personalised, titrated or adapted, then describe what, why, when, and how	7–9, 11–12 Supp. Appendix: 6–7		If the placebo/sham intervention was planned to be personalised, titrated or adapted, then describe what, why, when, and how	7–9, 11–12 Supp Appendix: 6–7	
10 Modifications					
If the intervention was modified during the course of the study, describe the changes (what, why, when, and how)	15 Supp. Appendix: 37	COVID-19 pandemic caused one individual to not receive biofeedback during their final 9-month training visit.	If the placebo/sham intervention was modified during the course of the study, describe the changes (what, why, when, and how)	15 Supp. Appendix: 37	COVID-19 pandemic caused one individual to not receive biofeedback during their final 9-month training visit.
11 How well: planned					
Planned: If intervention adherence or fidelity was assessed, describe how and by whom, and if any strategies were used to maintain or improve fidelity, describe them	17 Supp. Appendix: 15		Planned: If placebo/sham intervention adherence or fidelity was assessed, describe how and by whom, and if any strategies were used to maintain or improve fidelity, describe them	17 Supp. Appendix: 15	
12 How well: actual					
Actual: If intervention adherence or fidelity was assessed, describe the extent to which the intervention was delivered as planned	Supp. Appendix: 17, 24–26		Actual: If placebo/sham intervention adherence or fidelity was assessed, describe the extent to which the intervention was delivered as planned	Supp. Appendix: 17, 24–26	
13 Measuring the success of blinding					
Was blinding measured, and if so: how, and what were the results of such measurement?	11, 21	The blind was not assessed.			

Initial Protocol

In the following sections, we present the grant proposal, clinicaltrials.gov protocol, and Institutional Review Board protocol in original, unedited form. However, some information in these documents may not perfectly represent how the trial was conducted. The protocol described in the Supplementary Appendix: Protocol Summary and in the Methods is accurate to how the trial was conducted, and thus, supersedes any information in the grant, clinicaltrials.gov, and the Institutional Review Board protocol in the event of a minor discrepancy.

Grant Proposal

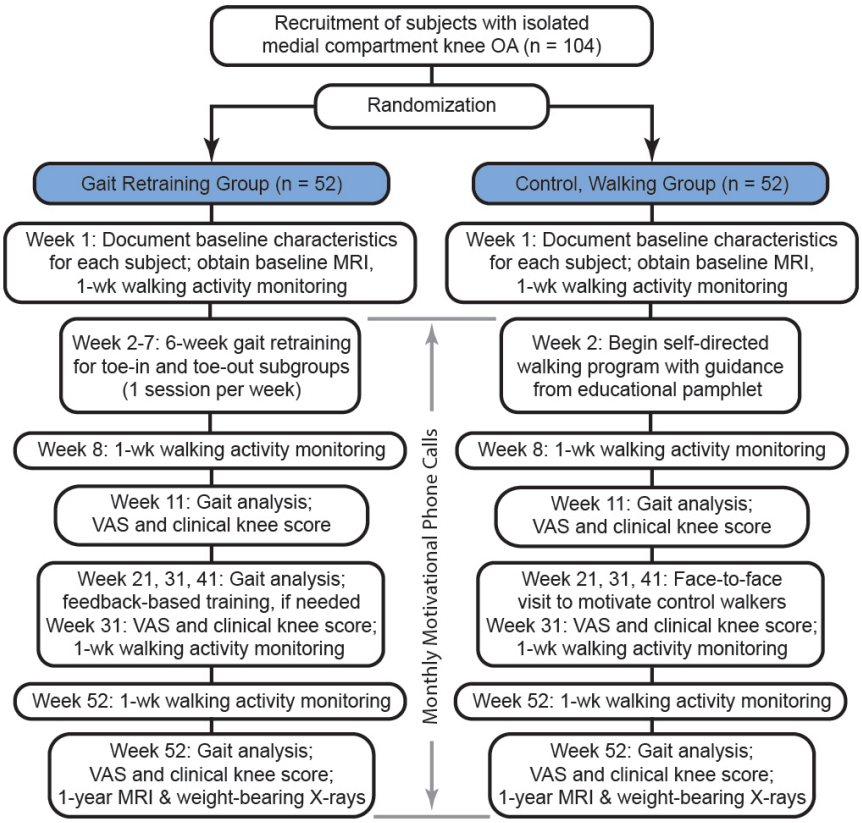
The original grant had two separate Aims. However, only Aim 2 is pertinent to the presented randomized controlled trial.

> ***"Aim 2: To test the hypothesis (H.2) that a 12-month gait training intervention that includes a targeted amount of daily walking will yield a significantly greater pain reduction compared to a control group with the same targeted amount of daily walking, but without any gait modification.*** *Participation in a community-based walking program has been shown to reduce pain in individuals with knee OA. Since gait retraining requires practice, i.e., daily walking using the modified gait, it is essential that the benefits of gait retraining program are compared to the benefits of a walking program alone. Because pain is a highly subjective measure, and because there is the potential of a placebo effect in both the gait retraining and control groups, it would be valuable to assess other measures of knee joint health that are objective and quantifiable. Therefore, in addition to the above primary aims, we will also pursue the following exploratory aims:* ***Exploratory Aim 1:*** *To test whether there will be reduced cartilage thinning detectable by Magnetic Resonance Imaging (MRI) after a 12-month intervention in the gait retraining group compared to the control group.* ***Exploratory Aim 2:*** *To test whether there will be changes in articular cartilage matrix composition and organization after a 12-month intervention in articular cartilage that are detectable using state-of-the-art MRI sequences (T1rho, DESS). If there are changes, we will then test whether those changes indicate any added benefit for gait retraining compared to the control intervention. "*

C. Research Design and Methods

C1. Methods

The following flow chart shows key project tasks and assessments:



To accomplish our specific aims we will begin by recruiting participants with medial compartment knee OA with the help of four collaborating clinicians (two VA orthopaedists, one VA rheumatologist, and one Stanford orthopaedist). A comprehensive list of the inclusion/exclusion criteria is given in section **4. Human Subjects**. Three key inclusion criteria for patients are: diagnosed with isolated, medial compartment knee OA of at least six months duration; Kellgren-Lawrence OA grade of I, II, or III; average knee pain of 30 mm or greater on a 100 mm visual analog scale. The average recruitment rate will be slightly less than 3 subjects per month during years 1, 2 and 3, with a total recruitment goal of 104 subjects. After signing an informed consent, each subject will be randomized (as described in section **C.3. Statistical Analysis**) to either the gait retraining group or the self-directed walking (control) group.

After randomization, we will document all subjects' baseline characteristics. These include: a gait analysis, a score of their knee pain using a visual analog scale (VAS), a clinical knee questionnaire (KOOS), an MRI, and their walking activity for one week (using a pedometer described later). In addition, each subject will have their knee mechanical axis measured from a weight-bearing, long-leg radiograph. Starting with week 2, subjects will participate in group-specific activities, described below, beginning with the gait retraining group.

Gait Retraining Group

For subjects assigned to the gait retraining group, the initial gait analysis will document each subject's baseline KAM profile, which in turn will determine the modification (relative toe-in vs. relative toe-out) each subject will be assigned. To determine the targeted amount of relative toe-in or toe-out for each subject, we will use an approach used previously by members of our research team. Each subject will walk at their normal (baseline) foot progression angle for 1 minute while kinematic and kinetic data are collected for each step. Then each subject will walk for 1 minute each at +5, +10, -5, and -10 degrees relative to their baseline foot progression angle. This 5-minute test generates approximately 300 data points for foot progression angle and peak KAM. The 300 data points for each subject will be fit with a linear regression, which, in preliminary studies, has always resulted in a significant correlation, with a coefficient of determination typically greater than 0·7 (*Shull, personal communication*). That linear regression will be used to determine the minimum change in foot progression angle that reduces the peak KAM by at least 10%.

During their baseline gait assessment, any individual who is found to have essentially equal 1st and 2nd KAM peaks will be assigned to either the toe-in or toe-out group based on the following strategy. We will test both toe-in and toe-out gait modifications and see which one results in the lowest peak KAM value, regardless of whether that new peak is the first or second. If we still have a tie with equal new KAM peaks for increased toe-in and increased toe-out gait, we will then see which choice leads to the largest reduction in the total area under the KAM curve (referred to as the KAM impulse). We expect that the double tie-breaker strategy will be needed for very few individuals.

The above procedure will determine to which subgroup (relative toe-in or relative toe-out) each subject will be assigned for the 52-weeks of gait retraining. In order to assess the benefit of personalizing the gait retraining, at their week 1 visit we will also conduct a gait analysis to determine what the effect would have been had each subject been assigned to the opposite subgroup (assigned to relative toe-in modification even though they had a larger second KAM peak, or assigned to relative toe-out even though they have a larger first KAM peak). For example, if a given subject is known to have a larger first KAM peak (and assigned to the toe- in subgroup), and their target gait modification requires a relative toe-in of 7 degrees, we will conduct a single gait analysis while that subject walks with a relative toe-out of 7 degrees. This will allow us to answer the question of what would the effect be if we prescribed a relative toe-in gait modification for all subjects. We will use a test of proportions to determine if more subjects benefit from the personalized assignment into two subgroups compared to requiring all subjects to toe-in.

Thus, for each subject who undergoes gait retraining we will know their baseline KAM characteristics, their KAM characteristics when assigned to the subgroup known to reduce their larger KAM, and their KAM characteristics when assigned to the subgroup which is unlikely to reduce the larger peak in their KAM profile.

Gait Retraining using Real-Time Feedback

Subjects in the gait retraining group will visit the Human Performance Laboratory at Stanford University once per week for six consecutive weeks to undergo gait retraining using real-time feedback to facilitate acquisition of the new gait pattern using the approach developed and tested by Shull et al. In brief, feedback will be administered using a wearable vibration device. The device will be a C-2 tactor motor (EAI, Casselberry, FL), which was used in preliminary studies and was chosen because of the capability to control vibration amplitude and frequency independently. The motor will be vibrated at 250 Hz, which is near the peak sensitivity of fast-acting mechanoreceptors in skin. The controller for the motor will be implemented using the Matlab

xPC operating system, and we will extract motion capture data from Motion Analysis' Cortex software in real-time as it is collected.

To measure kinematics during walking, a 3D motion capture system (Motion Analysis Corp., Santa Rosa, CA) will be used. Reflective markers will be attached to the subject and marker positions will be located in space via infrared cameras. Foot progression angle will be determined from markers attached above the 2nd metatarsal and in line with the center of the heel of each subject's shoe. Motion Analysis's Cortex software will be used to convert marker positions into a segmented biomechanical model, providing segment and joint positions and rotations in real-time through Motion Analysis' Software Developers Kit. Marker data will be collected at 60 Hz. Ground reaction forces and center of pressure measurements will be collected at 1200 Hz using an instrumented treadmill (Bertec Corp, Columbus, OH).

Real-time vibration feedback will be used to instruct changes to foot progression angle using the C-2 tactor motor, as described previously. Hypoallergenic double-sided tape will be used to adhere the motor to the skin. The tactor motor will be placed on the lateral–distal aspect of the fibula and vibrated once to indicate a required decrease in foot progression angle (more toe-in is needed) and twice to indicate a required increase in foot progression angle (more toe-out is needed). No vibration feedback will indicate that the foot progression angle is adequately close (±1·0 degrees, based on the precision found in our preliminary studies) to the target value. Feedback will be given on each step.

The percent of training time that feedback will be given during each of the six training sessions will decrease from week to week, according to a fading feedback protocol. We, and others, have used a fading feedback design to encourage internalization of the new gait pattern. The goal is that the new gait feels increasingly natural and becomes the default gait pattern for each subject. Real-time feedback will be provided for 100% of the training time during the 1st and 2nd training sessions, 66% of the time during the 3rd and 4th training sessions, 50% of the time during the 5th training session, and 0% of the time during the final training session. Our preliminary study suggests that this fading feedback design is sufficient for subjects to begin to internalize the new gait pattern. A gait analysis conducted four weeks following the final training session (week 11) will assess the extent to which subjects can reproduce the new gait pattern. Subjects will also return for gait analysis checks at weeks 21, 31, and 41. If any of the gait analysis checks indicate that a subject has lost more than 3 degrees or 25%, whichever is greater, of his/her target toe-in/out change, then that subject will undergo gait refresher training with feedback, once per week for 4 weeks, with a similar fading feedback design as used during the initial gait retraining phase.

Self-Directed Walking Group

Subjects assigned to the self-directed walking (control) group will be given an educational pamphlet (included in the Appendix) distributed by the Arthritis Foundation to encourage daily walking as a way to reduce the symptoms from arthritis. These subjects will be encouraged to increase their walking by at least 10 minutes per day compared to their week 1 baseline amount. Apart from the gait retraining sessions, participants assigned to the walking control group will undergo the same evaluations received by the subjects in the gait retraining group.

Enhancing Subject Retention

Subjects in both groups will be encouraged via monthly phone calls to continue their regular walking activity. Subjects in the gait retraining group will be specifically encouraged to practice their new gait for at least 10 minutes per day. To further encourage subject retention, subjects that reach the 31-week time point will be given a $25 incentive reward. Subjects who complete the entire 12-month intervention will receive a $50 completion reward and be given an Omron HJ-323U pedometer to keep.

Imaging Assessment

Table G1: MRI Assessment

Sequence	Scan Time (min)	Morphology/Physiology Objective
3D T1rho	8	Cartilage Matrix Properties (GAG, collagen)
3D DESS	11	Cartilage Thickness Cartilage T2 map (collagen) Apparent Diffusion Coef. (ADC) map (GAG)

Magnetic Resonance Imaging (MRI) will be used for cartilage assessments using 3D T1rho and 3D modified DESS sequences. The imaging protocols at 3·0T for each subject are outlined in Table G1. Subjects will be scanned using an eight-channel, phased-array knee coil. Subjects will also have a weight-bearing knee X-ray at the 52-week time point. This will be used in conjunction with their clinical weight- bearing X-ray at entry into the study to assess changes in the K-L OA grade.

The T1rho images will allow us to investigate if articular cartilage matrix changes can be detected within 12 months and if there are regional differences in T1rho between the gait retrained group and the walking control group. We will analyze the T2 maps obtained from the DESS sequence to assess regional variations of the collagen matrix. The Apparent Diffusion Coefficient from the DESS sequence is anticipated to show greater sensitivity to changes in the GAG matrix, so this may provide an early

indication of matrix change. Finally, the DESS sequence will be used to assess changes in cartilage thickness with time and differences in cartilage thickness between groups.

Given the lack of data on MRI detectable changes to cartilage over a 12-month time frame for this type of gait retraining intervention, it is possible that we will not be able to detect early changes in cartilage thickness or physiological properties. Such changes will be more easily detected at longer assessment time points. Although not formally a part of our outcome measures, we plan to include a provision in the informed consent that will allow us to contact subjects after they complete their 12-month participation. If the VA 3T MRI scanner schedule can accommodate additional non-clinical scans (or if VA Palo Alto is successful in acquiring a second 3T scanner for research use), we will attempt to rescan subjects recruited during year one at their 24- and 36-month time points. All subjects recruited during year two will be asked to have repeat scans at their 24-month time point. In this way, we may be able to collect longer term MRI data for up to two-thirds of the original cohort.

Patient Knee Assessments

The Knee injury and Osteoarthritis Outcome Score (KOOS) knee score and VAS will be evaluated at five time points: start of study; after the final gait retraining session (week 7); at the four-week, post-training follow-up (week 11); at the 31-week gait analysis check, and at the end of study (week 52).

Assessment of Walking Activity

To obtain a quantitative assessment of each subject's walking history, we will record daily step totals for seven consecutive days during week 1, week 8, week 31, and week 52 of each subject's 52-week participation. Each subject will be issued a tri-axial, accelerometer-based pedometer (Omron HJ-323U, Omron Healthcare, Lake Forest, IL) and instructed in its use. When mounted at the waist, tri-axial Omron pedometers have been shown to be both reliable and valid for counting steps during walking, as well as stair ascent and descent. The HJ-323U measures steps on a day-by-day basis, for up to 22 days. Step counts are automatically stored in memory at midnight each day and the display count is then automatically reset to zero for the next day. Apart from attaching the pedometer each day, no additional action is required by users. Stored data is eventually downloaded for analysis via a USB connection.

C.2. Expected Results

We expect that a larger proportion of subjects in the gait retraining group will achieve a reduction in their peak KAM because of their proper assignment into the relative toe-in or toe-out subgroup based on which peak is larger in their baseline KAM profile. The success of the personalized assignment will be determined by a two-sample test of proportions.

Based upon the findings from the preliminary studies of Shull et al., we expect the average reduction in peak KAM will exceed our initial 10% minimum target. We also expect that the reduction in KAM will improve with increasing training time, consistent with the difference in KAM reduction associated with one training session (13%) vs. 6 training sessions (20%) [16]. That improvement could be related to a gradual optimization of muscle recruitment or muscle activation that occurs as subjects become more accustomed to their new gait pattern.

Based on previous results reported in the literature on the benefits of walking for those with OA, we expect that subjects in both groups in our study will experience a reduction in knee pain. However, we expect that the reduction in pain for subjects in the gait retraining group will be significantly greater than the reduction in pain in the walking control group.

Based on our preliminary studies of toe-in gait modification, we expect to find a significant correlation between the change in foot progression angle and the percent reduction in KAM in the gait retrained group. Although not examined in our preliminary studies, we will also look for a correlation between the percent change in KAM and the reduction in pain.

It is difficult to predict what the expected results will be for the MRI-derived parameters to be examined in our exploratory hypotheses. Since gait retraining has a load altering effect at the knee, we expect that the rate of OA progression in those subjects will slow down. We do not know what to expect in the walking control group, since walking alone will not reduce joint loading, and therefore their expected reduction in pain cannot be associated with a reduction in loading. As a result we do not expect to see a clinically meaningful change in OA progression in the control group. However, if the expected trends in OA progression (slowing in the gait retrained group; no slowing in the walking group) are maintained with time, we would expect to be able to detect a group-by-time interaction in cartilage morphology and physiology given adequately long observation times. We believe that by measuring three different MRI parameters (T1rho, T2, and ADC [the latter two from DESS]) reflective of different aspects of cartilage physiology that we will increase the likelihood of finding at least one parameter that differs between groups.

Institutional Review Board – Initial

eProtocol # 37721 (New)
PD: Dr. Gary Beaupre
Review Type: Regular
Medical

PROTOCOL APPLICATION FORM Human Subjects Research Stanford University

Title : Long-Term Effectiveness of Walking Training in Patients with Knee Osteoarthritis
Approval Period: Draft

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CITI Training current				Y

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CITI Training current				

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CITI Training current				Y

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CITI Training current				

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CITI Training current				Y
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CITI Training current				Y
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CITI Training current				Y
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CITI Training current				Y
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CITI Training current				Y

Participant Population(s) Checklist	**Yes/No**
• Children (under 18)	N
• Pregnant Women and Fetuses	N
• Neonates (0 - 28 days)	N

Title : Long-Term Effectiveness of Walking Training in Patients with Knee Osteoarthritis
Approval Period: Draft

• Abortuses	N
• Impaired Decision Making Capacity	N
• Cancer Subjects	N
• Laboratory Personnel	N
• Healthy Volunteers	N
• Students	N
• Employees	N
• Prisoners	N
• Other (i.e., any population that is not specified above)	Y
• International Participants	

Please enter the countries separated by comma

Study Location(s) Checklist	Yes/No
• Stanford University	Y
• Clinical & Translational Research Unit (CTRU)	
• Stanford Hospital and Clinics	
• Lucile Packard Children's Hospital (LPCH)	
• VAPAHCS (Specify PI at VA)	Y

Beaupre, Gary S.

- Other (Click ADD to specify details)

General Checklist

Multi-site	Yes/No
• Is this a multi-site study? A multi-site study is generally a study that involves one or more medical or research institutions in which one site takes a lead role.(e.g., multi-site clinical trial)	N

Collaborating Institution(s)	Yes/No
• Are there any collaborating institution(s)? A collaborating institution is generally an institution that collaborates equally on a research endeavor with one or more institutions.	N

Cancer Institute	Yes/No
• Cancer-Related Studies (studies with cancer endpoints), Cancer Subjects (e.g., clinical trials, behavior/prevention) or Cancer Specimens (e.g., blood, tissue, cells, body fluids with a scientific hypothesis stated in the protocol).	N

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Clinical Trials	**Yes/No**
• Investigational drugs, biologics, reagents, or chemicals?	N
• Commercially available drugs, reagents, or other chemicals administered to subjects (even if they are not being studied)?	N
• Investigational Device / Commercial Device used off-label?	Y
• IDE Exempt Device (Commercial Device used according to label, Investigational In Vitro Device or Assay, or Consumer Preference/Modifications/Combinations of Approved Devices)	Y
• Will this study be registered on# clinicaltrials.gov? (See Stanford decision tree)	Y
• Who will register for ClinicalTrials.gov?NCT#	

Tissues and Specimens	**Yes/No**
• Human blood, cells, tissues, or body fluids (tissues)?	N
• Tissues to be stored for future research projects?	N
• Tissues to be sent out of this institution as part of a research agreement? For guidelines, please see https://sites.stanford.edu/ico/mtas	N

Biosafety (APB)	**Yes/No**
• Are you submitting a Human Gene Transfer investigation using a biological agent or recombinant DNA vector? Please review the Administrative Panel on BioSafety website for more information.	N
• Are you submitting a Human study using biohazardous/infectious agents? If yes, refer to the Administrative Panel on BioSafety website prior to performing studies.	N
• Are you submitting a Human study using samples from subjects that are known or likely to contain biohazardous/infectious agents? If yes, refer to the Administrative Panel on BioSafety website prior to performing studies.	N

Human Embryos or Stem Cells	**Yes/No**
• Human Embryos or Gametes?	N
• Human Stem Cells (including hESC, iPSC, cancer stem cells, progenitor cells)	N

Veterans Affairs (VA)	**Yes/No**
• The research recruits participants at the Veterans Affairs Palo Alto Health Care System(VAPAHCS).	Y
• The research involves the use of VAPAHCS non-public information to identify or contact human research participants or prospective subjects or to use such data for research purposes.	Y
• The research is sponsored (i.e., funded) by VAPAHCS.	Y

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- The research is conducted by or under the direction of any employee or agent of VAPAHCS (full-time, part-time, intermittent, consultant, without compensation (WOC), on-station fee-basis, on-station contract, or on-station sharing agreement basis) inconnection with her/his VAPAHCS responsibilities. Y
- The research is conducted using any property or facility of VAPAHCS. Y

Equipment **Yes/No**

- Use of Patient related equipment? If Yes, equipment must meet the standards established by Hospital Instrumentation and Electrical Safety Committee (650-725-5000) Y
- Medical equipment used for human patients/subjects also used on animals? Y
- Radioisotopes/radiation-producing machines, even if standard of care? http://www.stanford.edu/dept/EHS/prod/researchlab/radlaser/Human_use_guide.pdf More Info Y

Payment **Yes/No**

- Subjects will be paid/reimbursed for participation? See payment considerations. Y

Funding **Yes/No**

- Training Grant? N
- Program Project Grant? N
- Federally Sponsored Project? Y
- https://doresearch.stanford.edu/policies/research-policy-handbook/definitions-and-types-agreements/sponsored-Industry Sponsored Clinical Trial? N

Funding

Funding - Grants/Contracts

Funding Administered By :	VA	**SPO # (if available) :**	
Grant # (if available) :	1I01RX001811-01A2	**Funded By (include pending) :**	Department of Veterans Affairs
Principal Investigator :	Beaupre, Gary		

Grant/Contract Title if different from Protocol Title :
Personalized Gait Training with Feedback to Reduce Knee Pain from Osteoarthritis

Y For Federal projects, are contents of this protocol consistent with the Federal proposal?
N Is this a Multiple Project Protocol (MPP)?
N Is this protocol under a MPP?

Funding - Fellowships

Gift Funding

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Dept. Funding

Other Funding

Resources :

a) Qualified staff.

Please state and justify the number and qualifications of your study staff.

Gary Beaupre, PhD
Dr. Beaupre is the Principal Investigator and a VA Research Career Scientist. Dr. Beaupre has more than thirty years of experience in multiple research areas within the field of orthopaedic biomechanics and is a recognized international expert. Dr. Beaupre will be responsible for overall project management and for coordinating the work outlined in the proposed study. Dr. Beaupre will assure that all project personnel are appropriately trained in the techniques being used and all required safety measures are followed. Furthermore, he will be responsible for ensuring that research goals are met in a timely manner with scientific integrity, that work is done within the approved budget, and that all aspects of the research study are done in accordance with VA regulations.

Garry Gold, MD
Dr. Gold is a clinical musculoskeletal radiologist and researcher in magnetic resonance imaging (MRI) of osteoarthritis and musculoskeletal disease. He is a professor in the Department of Radiology at Stanford and a member of the VA Department of Radiology. Dr. Gold has nearly twenty years of experience designing and testing imaging protocols for studies of cartilage and joint disease and he leads several NIH-funded projects in this area. He will provide expertise on all imaging aspects of the project. He has substantial prior experience in projects with human subjects, including recruiting, consenting, data collection, analysis and data security.

Andrea Finlay, PhD
Dr. Finlay is a Research Health Scientist at the Center for Innovation to Implementation at the VA Palo Health Care System. Dr. Finlay has extensive experience in statistical design and analysis, with specific expertise in intent-to-treat analyses. Dr. Finlay will provide consulting assistance on any statistical issues that arise and she will contribute to the development of all presentations, reports, and publications derived from the analyses.

Scott Delp, PhD
Dr. Delp is the James H. Clark Professor of Bioengineering at Stanford University. Dr. Delp is an internationally recognized expert in neuro-musculo-skeletal biomechanics. Dr. Delp is the Co-Director of the Stanford Human Performance Laboratory (HPL) and one of the original team members who contributed to the preliminary studies of gait retraining with real-time haptic feedback which served as the foundation for the current study. He will serve in a comparable role during the planned project.

Amy Silder, PhD
Dr. Silder is Life Science Research Associate who works at the Stanford Human Performance Laboratory. Dr. Silder was one of the original team members who collected the motion capture and kinetic data for the preliminary studies of gait retraining with real-time haptic feedback which served as the foundation for the current study. She will serve in a comparable role during the planned project. She has substantial prior experience in projects with human subjects, including recruiting, consenting, data collection, analysis and data security.

Scott Uhlrich, MS
Mr. Uhlrich is a Stanford PhD student who has extensive experience in motion capture and gait retraining.

Mr. Uhlrich has experience in the collection of biomechanical data and analysis. He will assist in the collection of biomechanical data for the project.

Serena Bonaretti, PhD
Dr. Bonaretti is an Associate Specialist in the Department of Radiology at Stanford University. Dr. Bonaretti has extensive experience recruiting and consenting human subjects and performing musculoskeletal imaging research.

b) Training.

Describe the training you will provide to ensure that all persons assisting with the research are informed about the protocol and their research-related duties and functions.

All the personnel involved in the protocol are fully aware of the inclusion/exclusion criteria, the design, and the data being acquired. Each member of the research staff is experienced with human subjects research and is fully aware of HIPAA compliance and rules. The staff will read the protocol and will be trained regarding the protocol and their specific duties and functions by Dr. Beaupre. Staff will complete all trainings on proper research involving human subjects and on maintaining data security and subject confidentiality.

c) Facilities.

Please describe and justify.

Human Performance Laboratory, Stanford University
The Human Performance Laboratory (HPL) at Stanford University is a 2,500 square foot Core facility that supports interdisciplinary research in the fields of biomechanics, biomedical engineering, exercise physiology, orthopedics and rehabilitation. The HPL has the unique capability of being able to perform motion capture while individuals walk at constant speed, while continuously and simultaneously acquiring ground reaction forces from two independent force plates that are integrated into an instrumented split-belt treadmill system. Motion capture during treadmill walking will be accomplished with a 10-camera three-dimensional motion capture system.

Gait Laboratory at VAPAHCS
This is a motion capture laboratory located in Building T6 at the VAPAHCS. The Lab includes a ten camera Qualisys motion capture system along with multiple force plates, and is dedicated to the analysis of human movement. The Lab also includes office space and computer facilities.

Lucas Center, Stanford University
This large imaging research center has 3T scanners that are available for research imaging purposes and are configured to perform the advanced scans that will be performed in this study.

Radiology at VAPAHCS
The radiology department at the VAPAHCS has both MRI scanners and X-ray facilities and may be used to obtain lower limb radiographs and MRIs for the study.

Orthopaedic & Rheumatology Clinics at VAPAHCS and Stanford
Initial identification of potential subjects will be done by clinicians at VAPAHCS and Stanford. Prospective subjects will be instructed to contact a member of our research team for additional information about the project.

d) Sufficient time.

Explain whether you will have sufficient time to conduct and complete the research. Include how muchtime is required.

We propose to include 104 subjects over the course of 4 years who will complete a 52-week intervention. We expect to screen approximately 200 subjects in order to wind up with 104 subjects who complete the

intervention. Our team has the experience and the time commitment to ensure that the project remains on track to be completed within the proposed time frame.

e) Access to target population.

Explain and justify whether you will have access to a population that will allow recruitment of the required number of participants.

VA and Stanford Orthopaedic and Rheumatology clinicians will identify potential subjects meeting the inclusion and exclusion criteria at the time of their clinic visit. Departmental clinicians will notify potential subjects about the study and ask permission to have a clinical coordinator contact him/her with more information. If permission is granted, the clinical coordinator will follow-up in person at the clinic or by phone to answer any questions and to arrange for consenting. Based on discussions with the clinicians who staff the clinics in question we anticipate no problem recruiting the required number of subjects over the course of 4 years.

f) Access to resources if needed as a consequence of the research.

State whether you have medical or psychological resources available that participants might require as a consequence of the research when applicable. Please describe these resources.

We do not foresee any medical or psychological consequences as our research protocol poses minimal risks to our subjects. However, in the event of an unexpected emergency, medical or psychological, resources that participants might require are located at VA Palo Alto Health Care System and at the Stanford University Hospital and Clinics.

g) Lead Investigator or Coordinating Institution in Multi-site Study.

Please explain (i) your role in coordinating the studies, (ii) procedures for routine communication with other sites, (iii) documentation of routine communications with other sites, (iv) planned management of communication of adverse outcomes, unexpected problems involving risk to participants or others, protocol modifications or interim findings.

1. Purpose

a) In layperson's language state the purpose of the study in 3-5 sentences.

Nearly one out of every two Americans will develop kneeosteoarthritis by age 85. While a daily walking regimen is known to reduce pain from knee arthritis,gait retraining combined with walking has the potential to reduce excessive forceson the medial compartment of the knee, thereby slowing disease progression. Ourstudy will determine if gait training provides an additional benefit from walking that islong-lasting and leads to a greater pain reduction than walking alone.

b) State what the Investigator(s) hope to learn from the study. Include an assessment of the importance of this new knowledge.

The information obtained during this study will help advance
scientific and clinical
understanding of the effects of biomechanics on the progression and
novel conservative

treatment of knee osteoarthritis.

c) Explain why human subjects must be used for this project. (i.e. purpose of study is to test efficacy of investigational device in individuals with specific condition; purpose of study is to examine specific behavioral traits in humans in classroom or other environment)

The only way to test the hypothesis posed is by using human subjects, as the hypotheses of our study are directly related to the biomechanics of human locomotion and the benefits of walking as a conservative treatment for knee osteoarthritis. Animal models are not possible for the testing of our hypotheses.

2. Study Procedures

a) Please SUMMARIZE the research procedures, screening through closeout, which the human subject will undergo. Refer to sections in the protocol attached in section 16, BUT do not copy the clinical protocol. Be clear on what is to be done for research and what is part of standard of care.

The following lists all major research procedures. Each procedure is done for research; none is done as part of standard of care.

Recruitment, Screening, Randomization of Subjects: VA and Stanford Orthopaedic and Rheumatology clinicians will initially identify potential participants, who will then talk or meet with study investigators. Potential participants will be block randomized into one of two intervention arms by a study investigator (the differences in intervention arms can bee seen in "Haptic Feedback" Section below). Potential participants will be screened for eligibility and consented by a study investigator.

Knee MRI: Subjects will have a knee MRI scans at baseline and week 52. Longer-term, optional, follow-up MRI scans may be obtained at 24, 36, and 48 months.

Knee Radiographs: For subjects who do not have current clinical knee radiographs, research knee radiographs will be obtained at baseline. Follow-up research radiographs will be obtained at week 52. Optional radiographs may be taken at 24, 36, and 48 months.

Gait Analysis: Subjects will have gait analysis at weeks 2, 21, 35, 39 and 52. During those sessions we will record motion data, ground contact force data, and possibly muscle activation (EMG).

Gait Training: Subjects will undergo gait training using real-time haptic feedback (see description below) while walking on a treadmill. Gait training

will take place during weeks
2, 3, 4, 5, 6, and 7. Refresher training may take place during
weeks 11, 25 and 39.
Subjects will either be trained for foot progression angle
consistency or foot progression
angle modification.

Haptic Feedback: Haptic feedback will be administered through a
miniature, wearable
vibration motor or tactor. The tactor is attached to the skin with
Velcro or human-safe
adhesive tape and vibrates to give users feedback on a step-by-
step basis while walking.
The vibration motor is similar to the vibration motor inside most
cell phones. Haptic feedback will be used to give real time feedback
to
participants about the way that they walk. The only difference
between
the intervention arms is the foot angle that they are given feedback
to
achieve.

Pedometer & Smart Shoe Monitoring: Subjects will use a pedometer
and use smart shoes
during weeks 1, 7, 11, 25, 39 and 52.

Knee health questionnaire & VAS score: Subjects will complete the
KOOS clinical
questionnaire and asses their knee pain using a Visual Analog
Scale during weeks 1, 7,
11,25, 39 and 52.

Home and Community-Based Walking: Subjects will walk 10-minutes
per day
more than their historical average throughout the 52-week
intervention. Subjects will
maintain daily walking activity logs in which they record their
estimated number of walking
minutes per day.

b) Explain how the above research procedures are the least risky that can be performed consistent with sound research design.

The research protocol poses minimal risk to patients. All research
procedures are essential
for testing the hypotheses in the study and are consistent with
sound research design.

Risk from radiographs: The study-related radiographs will result
in an additional effective
dose equivalent of either 0.75 days or 1.5 days of natural
background radiation. Either
value represents a negligible risk.

Risks from MRI: MRI is non-invasive and non-ionizing. All subjects
will undergo screening

for metal in the body prior to MRI scanning. If the screeningindicates that potentially dangerous metal may be present, the subject will be excluded. TheMRI poses no more risk than that of a standard clinical MRI exam with FDA-approvedsequences.

Risks from gait analysis: Subjects will be asked to walk in awell-lit gait lab while wearing reflective markers. The collection of 3D motion capture data, EMGdata, and ground reaction forces are all non-invasive and pose minimal risk to theparticipants. There is no more risk to the subjects beyond the normal risks associated withwalking.

Risks from treadmill walking and gait training: While there is aminor risk of injury while walking on a treadmill, the likelihood and severity of an injuryis not greater than while walking on a treadmill in a gym. The treadmill has a safetyhandrail to reduce the risk of falling and the treadmill has an emergency stop button. The hapticdevices used for gait training vibrate on the skin like a cell phone vibrates and thusprovide little to no chance of injury.

Risk from VAS scoring: There is no risk to subjects from fillingout the Visual Analog Scale to assess knee pain.

Risks from questionnaire: There is no risk to subjects fromfilling out the clinical knee questionnaire.

Risk from pedometer: There is no risk to subjects from using apedometer to record steps while walking under free-living conditions.

Risk from use of Smart Shoes: Wearing the smart shoes poses nogreater risk to the subjects than wearing any new pair of athletic shoes. There is theminor risk of developing a
blister if they don't fit properly, but we will have an assortmentof sizes to offer to provide an
acceptable fit. Another minor risk is that the insole will have anarch that is not comfortable, but we will have an assortment of after-marketinsoles (Superfeet) in different sizes and styles if a subject feels the default arch isuncomfortable.

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Risk from additional walking under free-living conditions: There is no more risk to the
subjects beyond the normal risks associated with walking under free-living conditions.

c) State if deception will be used. If so, provide the rationale and describe debriefing procedures. Since you will not be fully informing the participant in your consent process and form, complete an alteration of consent (in section 13). Submit a debriefing script (in section 16).

Deception will not be used.

d) State if audio or video recording will occur. Describe what will become of the recording after use, e.g., shown at scientific meetings, erased. Describe the final disposition of the recordings.

Images and video recordings may be made while subjects perform research-related tasks in order to assist with subsequent data analysis. Images and video recordings may also be used at scientific meetings. Before any public use, images or videos will be fully de-identified, including masking of the subjects' faces. Images or video stored on portable media (e.g., USB flash drive, memory card, CD, DVD, tape) will be kept in a locked cabinet in a locked room accessible only to approved members of the research staff. Images and videos that may be saved indefinitely for scientific presentation will be kept on a secure server behind the VA firewall accessible only to approved members of the research staff.

e) Describe alternative procedures or courses of treatment, if any, that might be advantageous to the participant. Describe potential risks and benefits associated with these. Any standard treatment that is being withheld must be disclosed in the consent process and form. (i.e. standard-of-care drug, different interventional procedure, no procedure or treatment, palliative care, other research studies).

No standard treatment is being proposed or withheld.

f) Will it be possible to continue the more (most) appropriate therapy for the participant(s) after the conclusion of the study?

Yes. If we find convincing evidence for the long-term benefit of walking with either one's natural foot progression angle or with an altered foot progression angle, then subjects will be free to continue that practice after the conclusion of the study.

g) Study Endpoint. What are the guidelines or end points by which you can evaluate the different treatments (i.e. study drug, device, procedure) during the study? If one proves to be clearly more effective than another (or others) during the course of a study, will the study be terminated before theprojected total participant population has been enrolled? When will the study end if no important differences are detected?

A key objective of the study is assessing the persistence at 12 months (52 weeks) of a benefit from a regular walking regimen, both in a group that maintains their natural and consistent foot progression angle, and in a group that adopts an

altered foot progression
angle. Based on previous studies, we expect to see a benefit in
both groups at shorter time
points, however it is not know if those benefit remain at 12
months. By definition that
assessment requires evaluating the results at 12 months.

Given the lack of data on MRI detectable changes to cartilage over
a 12-month time frame
for this type of walking-based intervention, it is possible that
we will not be able to detect
early changes in cartilage thickness or physiological properties
via MRI. Such changes will
be
more easily detected at longer assessment time points. We will
include a provision in the
informed consent that will allow us to contact subjects after they
complete their 12-month
participation. We will attempt to rescan subjects enrolled during
year one at their 24 and
36-month time points. All subjects initially enrolled during year
two will be asked to have
repeat scans at their 24-month time point. In this way, we may be
able to collect longer
term
MRI data for up to two-thirds of the original cohort. For subjects
enrolled during year 3 it
may not be possible to scan them past the 12-month time point due
to the duration of
study
funding and staffing after the end of funding. Nevertheless, we
may be able to collect
longer
term MRI data for up to two-thirds of the original cohort.

3. Background

a) Describe past experimental and/or clinical findings leading to the formulation of the study.

Members of our research team previously demonstrated the
effectiveness of real-time,
haptic, gait retraining for individuals with knee OA in a six-week
pilot study that was
reported in the Journal of Orthopaedic Research (Shull et al., J
Orthop Res 31:1020-5,
2013).
Participating in a walking program for reducing pain for
individuals with OA has also been
shown to reduce knee pain in both 8-week (Kovar et al. 1992) and
12-week (Minor et al.,
1989; Peloquin et al.,1999) studies.

These studies lead us to believe that by maintaining one's natural
foot progression angle,

or by optimally modifying one's foot progression angle, when combined with additional daily walking, will have a short-term benefit and the goal of our study is to test whether that benefit will still be present at the end of a 52-week intervention.

b) Describe any animal experimentation and findings leading to the formulation of the study.

None.

4. Radioisotopes or Radiation Machines

a) List all standard of care procedures using ionizing radiation (radiation dose received by a subject thatis considered part of their normal medical care). List all research procedures using ionizing radiation (procedures performed due to participation in this study that is not considered part of their normal medical care). List each potential procedure in the sequence that it would normally occur during theentire study. More Info

Identify Week/Month of study	Name of Exam	Identify if SOC or Research
Week 1 (if needed)	Weight-Bearing Knee X-rays	Research
Week 52	Weight-Bearing Knee X-rays	Research
Month 24	Optional Weight-Bearing KneeX-rays	Research
Month 36	Optional Weight-Bearing KneeX-rays	Research
Month 48	Optional Weight-Bearing KneeX-rays	Research

b) For research radioisotope projects, provide the following radiation-related information:Identify the radionuclide(s) and chemical form(s).

N/A

For the typical subject, provide the total number of times the radioisotope and activity will be administered (mCi) and the route of administration.

N/A

If not FDA approved provide dosimetry information and reference the source documents (packageinsert, MIRD calculation, peer reviewed literature).

N/A

c) For research radiation machine projects, provide the following diagnostic procedures:For well-established radiographic procedures describe the exam.

Weight bearing x-rays of the knees will be taken for each subject to determine the condition of the cartilage and bone in the knee.

For the typical subject, identify the total number of times each will be performed on a singleresearch subject.

Up to two times per subject for the minimum 52 week participation. If subjects choose to partake in the 24, 36, and 48 month optional imaging sessions, the knee x-ray would be performed a maximum of 5 times.

For each radiographic procedure, provide the setup and technique sufficient to permit researchsubject

Whole body effective dose for a standard, clinical AP knee radiograph is documented on the www.radiologyinfo.org and in the archival literature (see below). The consensus effective dose is 1.0 microSv per knee per view. AP, ML, and notch radiographs of both knees at up to two times points would result in a combined effective dose of 12 microSv, equivalent to about 1.5 days of background radiation from natural sources. That effective dose poses a negligible lifetime risk of long-term harm.

Sources for Effective Dose of knee radiographs:

http://www.radiologyinfo.org/en/info.cfm?pg=safety-xray (accessed 04/26/16)

Huda W, Gkanatsios NA. Radiation dosimetry for extremity radiographs. Health Phys. 1998 Nov;75(5):492-9.

Okkalides D, Fotakis M. Patient effective dose resulting from radiographic examinations. Br J Radiol. 1994 Jun;67(798):564-72.

dose modeling. The chief technologist can usually provide this information.

For radiographic procedures not well-established, provide FDA status of the machine, andinformation sufficient to permit research subject dose modeling.

N/A

d) For research radiation machine projects, provide the following therapeutic procedures:

For a well-established therapeutic procedure, identify the area treated, dose per fraction and number of fractions. State whether the therapeutic procedure is being performed as a normal part of clinical management for the research participants's medical condition or whether it is being performed because

N/A

the research participant is participating in this project.

For a therapeutic procedure that is not well-established, provide FDA status of the machine, basisfor dosimetry, area treated, dose per fraction and number of fractions.

N/A

5. Devices

a) Please list in the table below all Investigational Devices (including Commercial Devices used off-label) tobe used on participants.

5. 1 Device Name : Smart Shoes Describe the device to be used.

Smart Shoes are standard athletic shoes with an encapsulated sensor embedded within the sole that measures and records the direction the toes point when walking.

Manufacturer: Custom built

Risk : Non-significant

Y I confirm the above are true.

Rationale for the device being non-significant risk:

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Wearing the smart shoes poses no greater risk than wearing any new pair of athletic shoes. There is the minor risk of developing a blister if they don't fit properly, but we will have an assortment of sizes to offer to facilitate an acceptable fit. Another minor risk is that the insole will have an arch that is not comfortable, but we will have an assortment of after-market insoles (Superfeet) in different sizes and styles if a subject feels the default arch is uncomfortable. If no size of shoe or insole proves to be acceptably comfortable, the subject will not be required to wear the smart shoes.

Sponsor of Project

Indicate who is responsible for submitting safety reports to the FDA:

Y The sponsor is a non-STANFORD investigator or group.

Ordering, Storage and Control

To prevent the device being used by a person other than the investigator, and in someone other than a research participant: Confirm that the device will be handled according to the SHC/LPCH policy for Investigational New Devices or as appropriate. If no, please provide an explanation. :

Y Confirm?

5. 2 Device Name : GE Signa Describe the device to be used.

MRI scanner

Manufacturer : **GE Healthcare**

Risk : **Non-significant**

Y I confirm the above are true.

Rationale for the device being non-significant risk:

Some of the RF coils, imaging accessories and equipment, and imaging software used to scan subjects at the Lucas Center are not FDA-approved.

The MR research being conducted requires highly specialized equipment and imaging software that does not exist in the clinical MR market so it is designed and manufactured by researchers at the Lucas Center and other hardware companies. Although some of the imaging software and equipment are not FDA approved, they have been tested for safety and are very similar to what is used regularly in clinical MR examinations. The MR personnel are highly trained in the set-up, utilization, and monitoring of this equipment.

Sponsor of Project

Indicate who is responsible for submitting safety reports to the FDA:

Y The sponsor is a non-STANFORD investigator or group.

Ordering, Storage and Control

To prevent the device being used by a person other than the investigator, and in someone other than a

research participant: Confirm that the device will be handled according to the SHC/LPCH policy for Investigational New Devices or as appropriate. If no, please provide an explanation. :

Y Confirm?

b) Please list in the table below all IDE Exempt Devices (Commercial Device used according to label,Investigational In Vitro Device or Assay, or Consumer Preference/Modifications/Combinations ofApproved Devices) to be used on participants.

5.1 Device Name : C2 Tactor

Describe the device to be used.

Wearable vibration device

Manufacturer Engineering Acoustics Inc. (EAI)

IDE Exemption

Y **This is a legally marketed device being used in accordance with its labeling.**

6. Drugs, Reagents, or Chemicals and Devices

a) Please list in the table below all investigational drugs, reagents or chemicals to be administered to participants.

b) Please list in the table below all commercial drugs, reagents or chemicals to be administered to participants.

7. Medical Equipment for Human Subjects and Laboratory Animals

If medical equipment used for human patients/participants is also used on animals, describe such equipment and disinfection procedures.

The bed/table and accessories that are used for the animals is different than the table humans use. Physiologic monitoring equipment is cleaned with a commercial disinfectant such as Roccal, Conflick, Sani-Wipes, or a 10% Bleach solution. All RF coils and positioning accessories are wrapped in plastic wrap or plastic bags for use with animals. Everything, even if it is animal use only, is cleaned with the above disinfectants after every use even if they are wrapped in plastic. The Lucas Center is checked yearly by several groups at Stanford who approve animal research in human systems: Stanford Health & Safety. We are reviewed by: Stanford APLAC panel; USDA; NIH; and Aaalac.

8. Participant Population

a) State the following: (i) the number of participants expected to be enrolled at Stanford-affiliated site(s); (ii)the total number of participants expected to enroll at all sites; (iii) the type of participants (i.e. students, patients with certain cancer, patients with certain cardiac condition) and the reasons forusing such participants.

(i) 200 subjects
(ii) 200 subjects
(iii) Subjects will have isolated, medial compartment, osteoarthritis of the knee with a Kellgren-Lawrence

grade of I, II, or III, of at least six months duration. These subjects are targeted because they have the best potential to benefit from a novel conservative treatment that involves increasing their habitual walking activity.

b) State the age range, gender, and ethnic background of the participant population being recruited.

Participants from age 18 to 80 will be recruited regardless of gender, race, and ethnic background.

c) State the number and rationale for involvement of potentially vulnerable subjects in the study (including children, pregnant women, economically and educationally disadvantaged, decisionally impaired, homeless people, employees and students). Specify the measures being taken to minimize the risks and the chance of harm to the potentially vulnerable subjects and the additional safeguards that have been included in the protocol to protect their rights and welfare.

N/A

d) If women, minorities, or children are not included, a clear compelling rationale must be provided (e.g., disease does not occur in children, drug or device would interfere with normal growth and development, etc.).

Our inclusion criteria specifically allows for the inclusion of women and minorities. Children will not be included since the study is funded by the Department of Veterans Affairs, which does not conduct research using children. In addition, children do not typically develop osteoarthritis.

e) State the number, if any, of participants who are laboratory personnel, employees, and/or students. They should render the same written informed consent. If payment is allowed, they should also receive

None

it. Please see Stanford University policy.

f) State the number, if any, of participants who are healthy volunteers. Provide rationale for the inclusion of healthy volunteers in this study. Specify any risks to which participants may possibly be exposed. Specify the measures being taken to minimize the risks and the chance of harm to the volunteers and the additional safeguards that have been included in the protocol to protect their rightsand welfare.

No participants will be healthy volunteers.

g) How will you identify and recruit potential participants about the research study? (E.g., by: Honest Broker or other https://researchcompliance.stanford.edu/participantengagement Research Participation services; chart review; treating physician; ads). All final or revised recruitment materials, flyers, etc. must be submitted to the IRB for review and approval before use. You may notcontact potential participants prior to IRB approval. See Advertisements: Appropriate Language for Recruitment Material.

Subjects (veterans and non-veterans) will first learn about the existence (but not specific study details) of the VA study of a new conservative treatment for medial compartment knee OA from a variety of sources, including word-of-mouth, their health care provider(s) at VA, or from other Bay Area clinicians (who are aware of the existence of the study via word-of-mouth), and posted flyers. We will also consider advertising via newspapers and the internet to achieve our recruitment targets. Any such ads will be submitted to the IRB for review and approval prior to use. Subjects interested in the study will only learn about specific study details after contacting a member of the VA research staff who has been trained to perform subject screening.

h) Inclusion and Exclusion Criteria.Identify inclusion criteria.

- Diagnosed with isolated, medial compartment knee OA of at least six months duration
- Kellgren-Lawrence grade of I, II, or III
- Age between 18 and 80 years at the time of enrollment
- Knee pain on at least 15 days of the previous month
- Average knee pain of at least 27.5, but less than 90.0 on a 100 mm visual analog scale
- Ambulatory without aids

- Able to walk for at least 25 consecutive minutes
- Able to reduce the prominent peak of the knee adduction moment by changing foot progression angle
- Able to give informed consent

Identify exclusion criteria.

- Body mass index equal to or greater than 35
- Pregnancy
- Plans for knee replacement within the next 12 months
- Contraindications to MRI
- Nerve or muscle disease associated with walking difficulty
- Narcotic pain medication usage
- History of rheumatoid arthritis, gout or pseudogout, or autoimmune disease
- History of neuropathic arthropathy, infectious disease, or other major systemic diseases
- History of symptomatic arthritis in lower limb joints other than the knees
- History of lower limb fracture or surgery requiring hospitalization
- Lateral tibiofemoral joint space width less than medial
- Mechanical knee symptoms (e.g., catching or locking) indicative of clinically significant meniscal pathology
- Significant meniscal or ligament pathology based on magnetic resonance imaging
- Physical examination findings of a positive McMurray or Apley test
- Recurrent giving way of the knee
- Finding of a positive Lachman test
- Positive anterior or posterior drawer test
- Symptoms originating from the patellofemoral joint
- Avascular necrosis
- History of knee buckling or recent (within two months) knee injury
- Replacement of any lower extremity joint
- Use of a hinged knee brace within the past six months
- Current or recent past use (within two months) of oral corticosteroids
- Severe knee malalignment of more than 5 degrees from neutral
- Intra-articular injection of corticosteroids within the past 2 months or planned for the next 12 months
- Intra-articular injection of hyaluronic acid within the past 2 months or planned for the next 12 months
- Cognitive impairments that would limit a subject's understanding

i) Describe your screening procedures, including how qualifying laboratory values will be obtained. If you are collecting personal health information prior to enrollment (e.g., telephone screening), please request a waiver of authorization for recruitment (in section 15).

Potential participants will initially be identified by VA and Stanford Orthopedic and Rheumatology clinicians. These clinicians will be familiar with the study's inclusion and exclusion criteria. Subsequent contact with potential participants by a study team member will confirm whether they meet the inclusion and exclusion criteria and to obtain contact information.

j) Describe how you will be cognizant of other protocols in which participants might be enrolled. Please explain if participants will be enrolled in more than one study.

Participants will be asked if they are enrolled in any other studies. Due to the minimal risk associated with this study, we do not see an additional risk to the participant enrolling in this study, even if he/she is enrolled in another study. However, we will not enroll subjects who are already enrolled in another study that involves a treatment for arthritis.

k) Payment/reimbursement. Explain the amount and schedule of payment or reimbursement, if any, that will be paid for participation in the study. Substantiate that proposed payments are reasonable and commensurate with the expected contributions of participants and that they do not constitute undue pressure on participants to volunteer for the research study. Include provisions for prorating payment. See payment considerations

Subjects will receive nominal payments of $100 after their 5th, 10th and 16th visit. In addition they will receive a $50 completion bonus after their 16th visit. This translate to less than $22 per visit.

After 52-weeks of participation subjects will also be offered an Omron pedometer to keep. The pedometer has a retail value of approximately $25.

l) Costs. Please explain any costs that will be charged to the participant.

None

m) Estimate the probable duration of the entire study. Also estimate the total time per participant for: (i) screening of participant; (ii) active participation in study; (iii) analysis of participant data.

The entire study is expected to be completed in 8 years including time for recruitment, data collection, follow-up, and data processing following IRB approval.

(i) Screening and consenting of each participants is expected to take 1.0 to 1.5 hours.

(ii) Active participation is expected to take approximately 20 hours over a total of 16 laboratory visits. Most visit times will take between 15 minutes and 1.25 hours. The 52 week visit will require 4 hours. In additional to laboratory visits, all subjects are expected to increase their habitual walking activity by 10 minutes per day over the entire 52-week intervention. It will be optional for subjects to receive follow-up x-rays and MRI scans at 24, 36, and 48 months. These visits will take 2 hours each and would increase their total participation time to 26 hours.

(iii) Analysis of data for each participant will require several days (participant not required to be present). Years 5-8 will be dedicated to follow-up MRI and x-ray visits, data synthesis, abstract, manuscript, and grant writing.

9. Risks

a) For the following categories include a scientific estimate of the frequency, severity, and reversibility of potential risks. Wherever possible, include statistical incidence of complications and the mortality rate of proposed procedures. Where there has been insufficient time to accumulate significant data on risk, a statement to this effect should be included. (In describing these risks in the consent form to the participant it is helpful to use comparisons which are meaningful to persons unfamiliar with medical terminology.)

The risks of the Investigational devices.

MRI: We will use some non-standard MRI sequences and coils; all will comply with FDA guidelines for safety and radio frequency power deposition. There are minimal risks associated with MRI including dizziness and nausea, heating and reddening of tattoos, heating of cables, claustrophobic sensations, and muscle twitching. If the participant reports any of these issues, the scan will be stopped. An additional risk of MRI is the strong magnet. Participants will be thoroughly screen prior to the scan to ensure they do not have any ferromagnetic materials in or on their person. None of the aforementioned risks are unique to the investigational nature of our sequences and coils, rather are a risk to all MRI procedures, investigational or clinical.

Smart Shoes: Wearing the smart shoes poses no greater risk to the subjects than wearing any new pair of athletic shoes. The "smart" component is a 2" x 1.5" x 0.5" thick insert that is encapsulated and embedded within the sole of the shoe. With the insoles inserted the shoes are indistinguishable from standard athletic shoes. There is a minor risk of developing a blister if the shoes don't fit properly, but we will have an assortment of sizes to offer subjects in order to provide an acceptable fit. Another minor risk is that the standard shoe insole will have an arch that is not comfortable, but we will have an assortment of after-market insoles (Superfeet) in different sizes and styles if a subject feels the default arch is uncomfortable.

The risks of the Investigational drugs. Information about risks can often be found in the Investigator's

brochure.

N/A

The risks of the Commercially available drugs, reagents or chemicals. Information about risks canoften be found in the package insert.

N/A

The risks of the Procedures to be performed. Include all investigational, non-investigational andnon-invasive procedures (e.g., surgery, blood draws, treadmill tests).

Risk from radiographs: The study-related radiographs will result in an additional effective dose equivalentof either 0·75 days or 1·5 days of natural background radiation. Either value represents a negligible risk.

Risks from MRI: MRI is non-invasive and non-ionizing. All subjects will undergo screening for metal in the body prior to MRI scanning. If the screening indicates that potentially dangerous metal may be present, the subject will be excluded. The MRI poses no more risk than that of a standard clinical MRI exam with FDA-approved sequences.

Risks from gait analysis & EMG: Subjects will be asked to walk in a well-lit gait lab while wearing reflective markers. There is no more risk to the subjects beyond the normal risks associated with walking. The application of the surface EMG electrodes might cause some skin irritation as the surface of the skin is prepared prior to the electrode placement with alcohol wipes and the electrode is adhered to the skin using double-sided tape. The tape is hypoallergenic to reduce the risk of skin irritation. Likewise, the application of reflective markers poses a similar risk of skin irritation as it uses the same double-sided tape to adhere the marker to the skin.

Risks from treadmill walking: While there is a minor risk of injury while walking on a treadmill, the likelihood and severity of an injury is not greater than while walking on a treadmill in a gym. The treadmill has a safety hand rail to reduce the risk of falling and the treadmill has an emergency stop button.

Risk from haptic feedback: The haptic device or tactor is designed to be incapable of causing an injury. The tactor is a small device, about the size of a quarter dollar in diameter, and 1/4 inch thick. It is taped to the skin or held with a Velco strap. Removing the tape might cause some momentary discomfort. During use, the tactor creates a buzzing feeling that is attention getting, but not uncomfortable.

Risk from VAS scoring: There is no risk to subjects from filling out the Visual Analog Scale to assess knee pain.

Risks from questionnaire: There is no risk to subjects from filling out the clinical knee questionnaire.

Risk from pedometer: There is no risk to subjects from using a pedometer to record steps while walking under free-living conditions.

Risk from use of Smart Shoes: Wearing the smart shoes poses no greater risk to the subjects than wearing any new pair of athletic shoes. There is the minor risk of developing a blister if they don't fit properly, but we will have an assortment of sizes to offer to provide an acceptable fit. Another minor risk is that the insole will have an arch that is not comfortable, but we will have an assortment of after-market insoles (Superfeet) in different sizes and styles if a subject feels the default arch is uncomfortable.

Risk from additional walking under free-living conditions: There is no more risk to the subjects beyond the normal risks associated with walking under free-living conditions.

The risks of the Radioisotopes/radiation-producing machines (e.g., X-rays, CT scans, fluoroscopy) and associated risks.

Risks of Radiographs: The effective dose (ED) of a single knee radiograph is 1 micoSv. Since an AP knee radiograph typically exposes both knees, the ED will be 2 microSv. The other four knee radiographic views will contribute a total of 4 microSv. Thus, for the baseline radiographs the total ED will be 6 microSv. The

radiographs at the 52-week time point will be an additional 6 microSv. The combined total ED for baseline and week-52 radiographs will be 12 mircoSv. The study-related radiographs will result in an ED equivalent to 1.5 days of natural background radiation, which represents a negligible risk. Note that the total ED will be only 6 microSv (0.75 days of background radiation) for subjects who already have recent (< 3 months old) clinical radiographs prior to entry into the study.

The risks of the Physical well-being.

The risks of the Psychological well-being.

None

The risks of the Economic well-being.

None

The risks of the Social well-being.

None

Overall evaluation of Risk.

Low - innocuous procedures such as phlebotomy, urine or stool collection, no therapeutic agent, or safe therapeutic agent such as the use of an FDA approved drug or device.

b) If you are conducting international research, describe the qualifications/preparations that enable youto both estimate and minimize risks to participants. Provide an explanation as to why the research must be completed at this location and complete the [LINKFORINTERNATIONALREASEARCHFORM] International Research Form. If not applicable,enter N/A.

N/A

c) Describe the planned procedures for protecting against and minimizing all potential risks. Include the means for monitoring to detect hazards to the participant (and/or to a potential fetus if applicable). Include steps to minimize risks to the confidentiality of identifiable information.

All subjects are free to withdraw at any time.

There is a potential risk of the strong magnetic field of the MRI scanner attracting ferromagnetic (material with a high magnetic permeability) or metallic objects toward the magnet. For this reason, subjects will be screened for metallic objects in their possession before entering the magnet room. All such metallic objects will be collected and placed in a locker outside of the magnet room. Subjects will also be screened for potentially dangerous metal in their body (e.g., shrapnel). Subjects who may have potentially dangerous metal in their body will be excluded from the study. During the scanning session, the magnet will make intermittent, loud, knocking noises that could cause ear discomfort in some people. Even though this noise is within safety levels, subjects will still be asked to wear ear-plugs (which will not interfere with their ability to communicate with the magnet operator) to minimize this discomfort. Women of child-bearing potential will take a urine pregnancy test prior to MRI. Pregnant women will be not be studied. Some people feel claustrophobic in the magnet; the study will be ended early if this is or becomes a problem for the study subject.

For individuals unaccustomed to walking on a treadmill, we will have them practice treadmill walking while holding onto the handrail until they feel comfortable walking on the treadmill.

During administration and completion of research related questionnaires, no identifiable information will be recorded, thus minimizing any privacy risk. There is no known risks associated with the completion of the

forms.

Research data for each subject will be identified by a code sequence and not by any patient identifiers. Linkage codes will be maintained in a locked filing cabinet in the locked office of the PI.

d) Explain the point at which the experiment will terminate. If appropriate, include the standards for the termination of the participation of the individual participant Also discuss plans for ensuring necessary medical or professional intervention in the event of adverse effects to the participants.

Experiments involving a specific subject will terminate anytime the subject wants to stop.

The study will terminate once data is collected from and processed for 104 subjects who have completed the entire 52-week intervention (estimated to take 4 to 5 years). It is possible that further analysis of the data will continue past that point, however, all of the data will be de-identified.

e) Data Safety and Monitoring Plan (DSMP). See guidance on Data Safety and Monitoring.

A Data and Safety Monitoring Plan (DSMP) is required for studies that present Medium or High risk to participants. (See Overall Evaluation of Risk above). If Low Risk, a DSMP may not be necessary. Multi-site Phase III clinical trials funded by NIH require the DSM Plan to have a Data Safety Monitoring Board or Committee (DSMC or DSMB). The FDA recommends that all multi-site clinicaltrials that involve interventions that have potential for greater than minimal risk to study participantsalso have a DSMB or DSMC.

The role of the DSMC or DSMB is to ensure the safety of participants by analyzing pooled data fromall sites, and to oversee the validity and integrity of the data. Depending on the degree of risk and thecomplexity of the protocol, monitoring may be performed by an independent committee, a board (DSMC/DSMB), a sponsor's Data Safety Committee (DSC), a Medical Monitor, a sponsor's safetyofficer, or by the Protocol Director (PD).

Describe the following:

What type of data and/or events will be reviewed under the monitoring plan, e.g. adverse events,

Adverse events and protocol deviations.

protocol deviations, aggregate data?

Identify who will be responsible for Data and Safety Monitoring for this study, e.g. Stanford Cancer Institute DSMC, an independent monitoring committee, the sponsor, Stanford investigators independent of the study, the PD, or other person(s).

Dr. Steven Woolson has agreed to constitute our Data Safety Monitoring Board (DSMB).

Provide the scope and composition of the monitoring board, committee, or safety monitor, e.g., information about each member's relevant experience or area of expertise. If the Monitor is the Stanford Cancer Center DSMC or the PD, enter N/A.

Since it is reasonable to describe our study as having minimal risk, we feel that the duties of a DSMB can be accomplished by a single individual. The person who has agreed to constitute our DSMB is Dr. Steven Woolson. Dr. Woolson is an attending physician at VA Palo Alto and Clinical Professor of Orthopaedic Surgery at Stanford University. Dr. Woolson has more than 30 years of clinical experience as an orthopaedic surgeon who specializes in the conservative and surgical treatment of patients with hip and knee arthritis. Dr. Woolson also is an accomplished researcher who is highly published and highly cited. Other than serving as our Data Safety Monitoring Board, Dr. Woolson will not otherwise be directly involved in the study. Dr. Woolson will review our interim data once 10 subjects have reached the 3-month point in the intervention, and quarterly thereafter.

Confirm that you will report Serious Adverse Events (SAEs), Suspected Unexpected Serious Adverse Reactions (SUSARs), or Unanticipated Problems (UPs) to the person or committee monitoring the study in accordance with Sponsor requirements and FDA regulations.

Confirmed.

Approval Period: Draft

If applicable, how frequently will the Monitoring Committee meet? Will the Monitoring Committee provide written recommendations about continuing the study to the Sponsor and IRB?

Dr. Woolson will review our safety data once 10 subjects have reached the 3-month point in the intervention, and quarterly thereafter.

Specify triggers or stopping rules that will dictate when the study will end, or when some action is required. If you specified this in Section 2g [Study Endpoints], earlier in this application enter 'See2g'.

See 2g

Indicate to whom the data and safety monitoring person, board, or committee will disseminate the outcome of the review(s), e.g., to the IRB, the study sponsor, the investigator, or other officials, as appropriate.

Dr. Woolson will disseminate the outcome of his reviews to the Principal Investigator and the IRB as appropriate.

Select One:

The Protocol Director will be the only monitoring entity for this study.

Y This protocol will utilize a board, committee, or safety monitor as identified in question #2 above.

10. Benefits

a) Describe the potential benefit(s) to be gained by the participants or by the acquisition of important knowledge which may benefit future participants, etc.

The information obtained during these studies will help advance medical research that could lead to improved conservative treatments for knee osteoarthritis (OA). Potential advantages include earlier treatment that changes the time course of OA progression. Based on our past studies of this type of gait training, and studies in the literature suggesting the benefits of increased walking, all subjects are expected to experience some reduction in knee pain.

11. Privacy and Confidentiality

Privacy Protections

a) Describe how the conditions under which interactions will occur are adequate to protect the privacy interests of participants (e.g., privacy of physical setting for interviews or data collection, protectionsfor follow-up interactions such as telephone, email and mail communications).

Initial identification of potential participants will be done by a patient's personal physician who will be familiar with our study or by a subject seeing a flyer or advertisement containing contact information for a study team member. Subsequent interactions with potential

participants by a approved member of the study team will occur by telephone for answering additional questions a potential participant might have, or in person in a private, laboratory setting, for any subject who prefers to meet in person.

Confidentiality Protections

b) Specify PHI (Protected Health Information). PHI is health information linked to HIPAA identifiers (see above). List BOTH health information AND HIPAA identifiers. If you are using STARR, use theData Privacy Attestation to ensure that your request will match your IRB-approved protocol. Be consistent with information entered in section 15a.

The following protected health information and individually identifiable information will be obtained from each subject: name; gender; social security number; date of birth; telephone number; address; height; weight; knee X-rays; knee MRIs; lower extremity health history; gait findings; VAS pain scale findings; knee health questionnaire findings.

For participants who are veterans and who are already entered into the VA Computerized Patient Record System (CPRS), we may access the participant's medical record to verify any medical conditions that may be relevant to the research study. For participants who are not veterans or not already entered into CPRS, the VA requires that we enter specific individually identifiable information about them. The information we are required to enter includes: name, gender, address, phone number, date of birth, and social security number. For all participants, certain dates may also be entered into CPRS, such as date of consenting, and date of X-rays or MRI. We may also acquire photographs or video of participants while performing any research-related tasks. This information will be stored on a secure VA server.

c) You are required to comply with University Policy that states that ALL electronic devices: computers (laptops and desktops; OFFICE or HOME); smart phones; tablets; external hard disks, USB drives, etc. that may hold identifiable participant data will be password protected, backed up, and encrypted.See http://med.stanford.edu/datasecurity/ for more information on the Data Security Policy and links to encrypt your devices.

Provide any additional information on ALL data security measures you are taking. You must use secure databases such as https://researchcompliance.stanford.edu/panels/hs/redcap RedCap. If you are unsure of the security of the system, check with your Department IT representative. Please see http://med.stanford.edu/irt/security/ for more information on IRT Information Security Services and http://www.stanford.edu/group/security/securecomputing/mobile_devices.html for more information for securing mobile computing devices. Additionally,any PHI data on paper must be secured in an locked environment.

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By checking this box, You affirm the aforementioned. Y

d) Describe how data or specimens will be labeled (e.g. name, medical record number, study number,linked

Any paper items containing PHI or III (e.g., linkage codes) will be kept in a locked filing cabinet in Dr. Beaupre's locked office at the VA, or in a locked filing cabinet in a locked room at the VA designated for the storage of human subjects documents (e.g., signed informed consent and HIPAA documents). Any electronic files containing PHI or III will be stored in an electronic folder assigned to Dr. Beaupre that is located on a secure VA server behind the VA firewall.

De-identified data in electronic format will be stored on a secure VA server behind the VA firewall or on password protected, encrypted Stanford computers. Collection of de-identified, coded data will occur on password-protected computers. Data analysis will only occur on de-identified data and will occur on password-protected computers.

coding system) or de-identified. If you are de-identifying data or specimens, who will be responsible for the de-identification? If x-rays or other digital images are used, explain how and bywhom the images will be de-identified.

All data for each subject will be identified by a unique code (see f below). All other identifiers will be removed. Dr. Beaupre or an approved study coordinator will provide the code to any study team member working with data needing to be de-identified. All knee MRIs and X-rays will be de-identified, coded, exported from the acquisition systems, and stored on a VA server behind the VA firewall. De-identified and coded MRIs and X-rays may also be stored on a secure Stanford server. De-identified photos and videos may also be stored on a VA server behind the VA firewall or on a secure Stanford server. These photos and videos will not include the face of the participant, or have it removed before storage for de-identification.

e) Indicate who will have access to the data or specimens (e.g., research team, sponsors, consultants) and describe levels of access control (e.g., restricted access for certain persons or groups, access to linked data

All members of the study team will have access to the de-identified (coded) data.

or specimens).

f) If data or specimens will be coded, describe the method in which they will be coded so that study participants' identities cannot be readily ascertained from the code.

When a participant enrolls in the study, they will be assigned a unique code number selected from a list of 200, non-repeated, 3-digit, random numbers (www.random.org/strings). All data for a given participant will be stored using their unique codenumber. Participants' identities will not be discernable from their code number.

g) If data or specimens will be coded, indicate who will maintain the key to the code and describe how itwill be protected against unauthorized access.

Dr. Beaupre will maintain the key to the code. The key will be stored in an electronic file stored on a secure VA server behind the VA firewall. The file with the key code will be password protected and only Dr. Beaupre and the study coordinator will have access to the file.

h) If you will be sharing data with others, describe how data will be transferred (e.g., courier, mail) or transmitted (e.g., file transfer software, file sharing, email). If transmitted via electronic networks, describe how you will secure the data while in transit.See http://www.stanford.edu/group/security/securecomputing/ http://www.stanford.edu/group/security/securecomputing/. Additionally, if you will be using or sharing

Data will not be shared outside of the study team.

PHI see https://uit.stanford.edu/security/hipaa https://uit.stanford.edu/security/hipaa.

i) How will you educate research staff to ensure they take appropriate measures to protect the privacy of participants and the confidentiality of data or specimens collected (e.g. conscious of oral and written communications, conducting insurance billing, and maintaining paper and electronic data)?

All members of the research team will complete all required trainings mandated by the research office - including all human subjects related research. Only the assigned subject code numbers will be used in all communications about individual data. In his regular meeting with the research team, Dr. Beaupre will discuss and reinforce the importance of privacy and data security.

12. Potential Conflict of Interest

Investigators are required to disclose any financial interests that " https://researchcompliance.stanford.edu/eprotocol-coi" target="_blank" reasonably appear to be related/li to thisprotocol.

Financial Interest Tasks

Investigators	Role	Potential COI?	Date Financial	Date OPACS Disclosure	COI Review Determination

			Interest Answered	**Submitted**	
Dr. Gary Beaupre	PD	N	05/05/2016	N/A	N/A
Scott L Delp	OP	N	05/05/2016	N/A	N/A
Garry Evan Gold	OP	N	05/06/2016	N/A	N/A

Title : Long-Term Effectiveness of Walking Training in Patients with Knee Osteoarthritis
Approval Period: Draft

13. Consent Background

13. 1 Consent

VA Consent Gait Training **Check if VA related** Y

a) Describe the informed consent process. Include the following.

i) Who is obtaining consent? (The person obtaining consent must be knowledgeable about the study.)

ii) When and where will consent be obtained?

iii) How much time will be devoted to consent discussion?

iv) Will these periods provide sufficient opportunity for the participant to consider whether or not to participate and sign the written consent?

v) What steps are you taking to minimize the possibility of coercion and undue influence?

vi) If consent relates to children and if you have a reason for only one parent signing, provide thatrationale for IRB consideration.

Dr. Beaupre or a member of his study team will obtain consent from participants. The subject will be assured that he/she has as much time as necessary to review the consent document and ask any questions. Any study team member who obtains consent will be fully trained in the consenting process and fully knowledgable about the study.

b) What is the Procedure to assess understanding of the information contained in the consent? How will the information be provided to participants if they do not understand English or if they have a hearing impairment? See HRPP Chapter12.2 for guidance.

The person obtaining consent will ask the participant if he/she has questions about the information contained in the consent or about the study. We do not expect to enroll anyone with whom there will be difficulty communicating nor will we enroll any non-English speakers and this will be determined from the initial contact.

c) What steps are you taking to determine that potential participants are competent to participate in the decision-making process? If your study may enroll adults who are unable to consent, describe (i) howyou will assess the capacity to consent, (ii) what provisions will be taken if the participant regains the capacity to consent,(iii) who will be used as a legally authorized representative, and (iv) what provisions will be

We will not recruit subjects who are unable to consent. Subjects will arrange for their own transportation to the study location. There is therefore sufficient reason to believe that they will be participating at their own free will. The research team will repeatedly remind the subject that they may withdraw at any time. To assess their capacity to consent, the research team will pause throughout the consent process to ask for understanding. Before obtaining consent, the team will ask the subject to state the activities and associated risks that would be consenting to in order to ensure that they are competent to consent.

made for the assent of the participant.

Additional VA questions:

i) List the people to whom you have formally delegated responsibility to obtain informed consent, andstate whether they have the appropriate training to perform this activity.

Dr. Beaupre, Dr. Silder, or Mr. Uhlrich will obtain all consents. These people have or will have completed appropriate training and each will have prior experience or specific training in performing consents.

ii) Will legally effective informed consent be obtained from the participant or the participant's legally authorized representative (LAR) or both? If LAR, is it clear who can serve as LAR?

Legally effective informed consent will be obtained from each participant. No LARs will be used.

iii) Will the circumstances of the consent process minimize the possibility of coercion or undue influenceand provide the prospective participant or their representative sufficient opportunity to consider whether to

Yes

participate?

iv) Will the circumstances of the consent process minimize the possibility of coercion or undue influence?

Yes

v) Will the information being communicated to the participant or the representative during the consent process exclude any exculpatory language through which the participant or the representative is madeto waive or appear to waive the participant's legal rights, or release or appear to release the investigator, the sponsor, the institution, or its agent from liability for negligence (e.g. I give up any property rights I may have in bodily fluids or tissue samples obtained in the course of the research)?

Yes

vi) Please confirm the following:

a. A witness to the participant's signature or the participant's legally authorized representative'ssignature will sign and date the consent document.

b. If the sponsor or the IRB requires a witness to the consenting process in addition to the witness tothe participant's signature and if the same person is needed to serve both capacities, a note to thateffect is placed under the witness's signature line.

c. A copy of the signed and dated consent document will be given to the person signing the consent document.

d. The consent form is on the VA Form 10-1086.

13. 2 Waiver of Documentation Phone ScriptCheck if VA related

a) Describe the informed consent process. Include the following.

i) Who is obtaining consent? (The person obtaining consent must be knowledgeable about the study.)

ii) When and where will consent be obtained?

iii) How much time will be devoted to consent discussion?

iv) Will these periods provide sufficient opportunity for the participant to consider whether or not to participate and sign the written consent?

v) What steps are you taking to minimize the possibility of coercion and undue influence?

vi) If consent relates to children and if you have a reason for only one parent signing, provide thatrationale for IRB consideration.

(i) Gary Beaupre, the Protocol Director or his research staff in the Human Performance Lab will be conducting the phone screen. (ii) Verbal consent for collecting information over the phone will be obtained before initiating the phone screen. (iii) 5 minutes at the beginning of the phone call. (iv) Yes. (v) The phone screener will assure the potential subject that their willingness to participate in the phone screen will have no bearing on their routine medical treatment. (vi) N/A

b) What is the Procedure to assess understanding of the information contained in the consent? How will the information be provided to participants if they do not understand English or if they have a hearing impairment? See HRPP Chapter12.2 for guidance.

The phone screen will only include subjects who can understand English and do not have a hearing impairment.

c) What steps are you taking to determine that potential participants are competent to participate in the decision-making process? If your study may enroll adults who are unable to consent, describe (i) howyou will assess the capacity to consent, (ii) what provisions will be taken if the participant regains the capacity to consent,(iii) who will be used as a legally authorized representative, and (iv) what provisions will be made for the assent of the participant.

Before continuing to the screening questions, we will ensure that the participant understands the risks of the phone screen and understands the screening activity. This will be judged by a conversation before asking the subject if they agree to participate in the screening procedure.

Select ALL of the following regulatory criteria for a waiver of documentation (signature) and provide aprotocol-specific justification:

1) 45 CFR 46·117(c)(i)., that the only record linking the participants and the research would be the consent document, and the principal risk would be potential harm resulting from a breach of confidentiality; each participant (or legally authorized representative) will be asked whether he/she wants documentation linking the participant with the research, and the participant's wishes govern.

2) 45 CFR 46·117(c)(ii)., that the research presents no more than minimal risk of harm to participants and involves no procedures for which written consent is normally required outsideof the research context.

3) **45 CFR 46·117(c)(iii)., if participants or legally authorized representatives (LAR) are membersof a distinct cultural group in which signing forms is not the norm, the research presents no more than minimal risk and there is an appropriate alternative mechanism for documenting that informed consent was obtained.**

4) Y **21 CFR 56·109(c)(1)., presents no more than minimal risk of harm to participants and involvesno procedures for which written consent is normally required outside of the research context.**

Rationale for above selection:

This phone screen poses minimal risk to the participant. The only potential harm is a breech in confidentiality, however the only recorded information will be a name, phone number, and email address. If the subject decides to participate in the study, this information will be stored securely. If the subject does not decide to participate, the information will be destroyed.

14. Assent Background (less than 18 years of age)

15. HIPAA Background

15. 1 Waiver of Authorization for Recruitment

waiver of authorization for recruitment

a) **Describe the protected health information PHI needed to conduct screening or recruitment. PHI is health information linked to HIPAA identifiers. List BOTH health information AND HIPAA identifiers. If you are using STARR, use the Data Privacy Attestation to ensure that your request willmatch your IRB-approved protocol.**

Potential volunteers for this study might leave a name, telephone number, and email address so we can contact them to arrange a suitable time for testing (these are the HIPAA identifiers). Pre-screening of potential participants will likely be done by phone to confirm that they meet the inclusion and exclusion criteria, and to obtain contact information. The health information that will be collected during this phone conversation can be seen in the attached phone script. It is an abbreviated version of the inclusion/exclusion criteria.

b) Please Answer:

Y **Do you certify that the use or disclosure of protected health information involves no more than aminimal risk to the privacy of individuals?**

Y **Do you certify that the research could not practically be conducted with out the waiver?**

Y **Do you certify that you have adequate written assurances that the protected health information willnot be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research project, or for other research for which the use or disclosure of protected health information would be permitted?**

Y **Do you certify that the research could not practically be conducted with out access to and use of theprotected health information?**

c) **Please describe an adequate plan to protect any identifiers from improper use and disclosure.**

All identifiers will be maintained on a password protected computer within the VA firewall.

d) **Please describe an adequate plan to destroy the identifiers at the earliest opportunity consistent withconduct of the research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law.**

All VA research records will be maintained consistent with existing VA record retention policies.

15. 2 Authorization va hipaa gait training

16. Attachments

Attachment Name	Attached Date	Attached By	Submitted Date
KOOS Questionnaire	05/18/2016	beaupre1	
Walking Activity Log	05/18/2016	beaupre1	
VA Required Questions, Gait Training	05/19/2016	beaupre1	
Full-Sized Flyer	06/13/2016	beaupre1	
Full-Sized Flyer with Tear-Offs	06/13/2016	beaupre1	
Quarter-Sized Flyer	06/13/2016	beaupre1	
VA Gait Training Grant	07/14/2016	suhlrich	

Obligations

The Protocol Director agrees to:

- Adhere to principles of sound scientific research designed to yield valid results
- Conduct the study according to the protocol approved by the IRB
- Be appropriately qualified to conduct the research and be trained in Human Research protection, ethicalprinciples, regulations, policies and procedures
- Ensure all Stanford research personnel are adequately trained and supervised
- Ensure that the rights and welfare of participants are protected including privacy and confidentiality of data
- Ensure that, when de-identified materials are obtained for research purposes, no attempt will be made tore-identify them.
- Disclose to the appropriate entities any potential conflict of interest
- Report promptly any new information, modification, or unanticipated problems that raise risks toparticipants or others
- Apply relevant professional standards.

Any change in the research protocol must be submitted to the IRB for review prior to the implementation of such change. Any complications in participants or evidence of increase in the original estimate of risk shouldbe reported at once to the IRB before continuing with the project. Inasmuch as the Institutional Review Board (IRB) includes faculty, staff, legal counsel, public members, and students, protocols should be writtenin language that can be understood by all Panel members. The investigators must inform the participants of any significant new knowledge obtained during the course of the research.

IRB approval of any project is for a maximum period of one year. For continuing projects and activities, it isthe responsibility of the investigator(s) to resubmit the project to the IRB for review

and re-approval prior tothe end of the approval period. A Notice to Renew Protocol is sent to the Protocol Director 7 weeks prior to the expiration date of the protocol.

https://stanfordmedicine.box.com/shared/static/qbsi8u8h47qsotxhdpuzz50xlrqa0sgo.pdf Report promptly any new information, complaints, possibly serious and/or continuing noncompliance, or unanticipated problems involving risks to participants or others.

All data including signed consent form documents must be retained for a minimum of three years past the completion of the research. Additional requirements may be imposed by your funding agency, your department, or other entities. (Policy on Retention of and Access to Research Data, Research Policy Handbook,
http://doresearch.stanford.edu/policies/research-policy-handbook/conduct-research/retention-and-access-research-data)APPROVAL LETTER/NOTICE NOTE: List all items (verbatim) that you want to be included in your
approval letter (e.g., Amendment date, Investigator's Brochure version, consent form(s) version(s), advertisement name, etc.) in the box below.

Consent Form
Advertisements
Waiver of Individual Authorization for recruitment under 45 CFR 164.512(i)(2)(ii)(A),(B),(C), pursuant to information provided in the HIPAA section of the protocol application.
Include grant title: Personalized Gait Training with Feedback to Reduce Knee Pain from Osteoarthritis

Y By checking this box, I verify that I, as the Protocol Director (PD) responsible for this research protocol, have read and agree to abide by the above obligations, or that I have been delegated authority by the PD tocertify that the PD has read and agrees to abide by the above obligations

clinicaltrials.gov – Initial

Study Identification

Unique Protocol ID: O1811-R

Brief Title: Long-Term Effectiveness of Walking Training in Patients With Knee Osteoarthritis

Official Title: Personalized Gait Training With Feedback to Reduce Knee Pain From Osteoarthritis

Secondary IDs:

Study Status

Record Verification: June 2016

Overall Status: Not yet recruiting

Study Start: November 2016

Primary Completion: October 2020 [Anticipated] Study Completion: October 2020 [Anticipated]

First Submitted: May 4, 2016

First Submitted that Met QC Criteria: May 6, 2016

First Posted: May 10, 2016 [Estimate]

Last Update Submitted that Met QC Criteria: June 10, 2016

Last Update Posted: June 14, 2016 [Estimate]

Sponsor/Collaborators

Sponsor: VA Office of Research and Development

Responsible Party: Sponsor

Collaborators:

Oversight

U.S. FDA-regulated Drug: U.S. FDA-regulated Device:

Data Monitoring: No

Study Description

Brief Summary: Nearly one out of every two Americans will develop knee osteoarthritis by age 85. Over 20 million Americans, including nearly three million Veterans, currently have painful knee arthritis that limits their daily activity or recreation. The vast majority of those individuals will be prescribed anti-inflammatory drugs that provide some pain relief but do not slow the progression of the disease. Often people with knee arthritis are told they must live with the pain until they become appropriate candidates for knee replacement surgery, but that can require tolerating the pain and limiting function for many years. Because of other health issues, some individuals are never acceptable surgery candidates. What is desperately needed are better conservative approaches for treating these patients. Two such approaches will be tested and compared in this study.

Detailed Description: This study is a randomized controlled trial to investigate conservative treatments for individuals with painful knee osteoarthritis (OA). The study will recruit participants who have isolated, medial compartment knee OA. Subjects will be assigned to one of two gait training
groups. Both groups will undergo gait analysis to determine their foot progression angle at their comfortable walking speed. Both groups will receive personalized gait retraining to either alter their foot progression angle or to achieve consistency of their natural foot progression angle.

Gait retraining will consist of once a week sessions for six weeks. The gait training will use a fading feedback approach, where the percentage of each weekly session during which feedback is used is decreased from week to week until no feedback is used by the last training session. Throughout the six-week training period subjects will be encouraged to practice their gait for at least ten minutes per day. Subjects will continue to practice their gait throughout the remainder of the 52-week intervention. Subjects will have their
walking activity recorded using a 3-axis pedometer, and smart shoes that will log their foot progression angle under free-living conditions.

Compared to their baseline walking activity, participants will be instructed to increase their daily walking by ten minutes per day throughout the 52-week intervention.

All subjects will receive monthly phone calls to encourage maintaining a regular walking regimen. Walking activity will be monitored periodically using a pedometer. Subjects will receive knee MRIs and weight-bearing knee radiographs at the start and end of the study. All participants will complete visual analog pain evaluations and clinical knee score questionnaires during the study. The investigators expect that subjects in both groups will have a reduction in knee pain over the course of the 52-week intervention. The primary objective of the study it to determine if there is change in pain between baseline and week 52 is different between the two groups.

Conditions

Conditions: Osteoarthritis

Keywords: Osteoarthritis, Knee
Arthritis
Joint Diseases
Musculoskeletal Diseases
Rheumatic Diseases

Study Design

Study Type: Interventional

Primary Purpose: Treatment

Study Phase: Phase 2

Interventional Study Model: Parallel Assignment

Number of Arms: 2

Masking: Single (Participant) Allocation: Randomized Enrollment: 104 [Anticipated]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Gait Training; Altered Foot Progression Angle Participants will receive personalized gait training while walking on a treadmill with real-time, haptic feedback. The goal of the training is to encourage participants to adopt an altered foot progression angle in an attempt to alter the distribution of forces crossing the knee joint. Training will occur once a week for six weeks. This will be followed by a 46-week home and community-based walking program to practice and internalize the new personalized, gait pattern and to encourage daily walking. Refresher training with haptic feedback will be offered at weeks 11, 25 and 39 to enhance internalization of the new foot progression angle.	Gait Training; Altered Foot Progression Angle Participants will receive personalized gait training while walking on a treadmill with real-time, haptic feedback to encourage them to adopt a new foot progression angle. Participants will walk for an additional ten minutes per day to internalize their new foot progression angle over 52 weeks.
Experimental: Gait Training; Consistent Foot Progression Angle Participants will receive personalized gait training while walking on a treadmill with haptic feedback. The goal of the training is to encourage participants to maintain a consistent foot progression angle in an attempt to minimize the variability in the forces crossing the knee joint. Training will occur once a week, for 6 weeks. This will be followed by a 46-week home and community-based walking program to encourage daily walking. Refresher training with haptic feedback will be offered at weeks 11, 25 and 39 to maintain foot progression angle consistency.	Gait Training; Consistent Foot Progression Angle Participants will receive personalized gait training while walking on a treadmill with haptic feedback to encourage them to maintain a consistent foot progression angle. Participants will walk an additional ten minutes per day to internalize the consistency of their foot progression angle over 52 weeks.

Outcome Measures

Primary Outcome Measures:

1. Knee adduction moment

[Time Frame: Change between baseline and week 52]

Change in magnitude of the more prominent peak in the knee adduction moment profile between baseline and week 52

2. Pain

[Time Frame: Change between baseline and week 52]

Visual Analog Scale for knee pain assessed

Secondary Outcome Measures:

1. Cartilage thinning

[Time Frame: Change between baseline and week 52]

Change in cartilage thickness between baseline and week 52

2. Cartilage MRI properties

[Time Frame: Change between baseline and week 52]

Change in cartilage properties assessed via MRI between baseline and week 52

☐ Eligibility

Minimum Age: 18 Years

Maximum Age: 80 Years

Sex: All

Gender Based: Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Diagnosed with isolated, medial compartment knee OA of at least six months duration
- Kellgren-Lawrence grade of I, II, or III
- Age between 18 and 80 years at the time of enrollment
- Knee pain on at least 15 days of the previous month
- Average knee pain of at least 27·5 mm, but less than 90·0 mm, on
- a 100 mm visual analog scale
- Ambulatory without aids
- Able to walk for at least 25 consecutive minutes
- Able to reduce the prominent peak knee adduction moment by
- changing foot progression angle
- Able to give informed consent
- Exclusion Criteria:

- Body mass index equal to or greater than 35
- Pregnancy
- Plans for knee replacement within the next 12 months
- Contraindications to MRI
- Nerve or muscle disease associated with walking difficulty
- Narcotic pain medication usage
- History of rheumatoid arthritis, gout or pseudogout, or autoimmune disease
- History of neuropathic arthropathy, infectious disease, or other major systemic diseases
- History of symptomatic arthritis in lower limb joints other than the knees
- History of lower limb fracture or surgery requiring hospitalization
- Lateral tibiofemoral joint space width less than medial Mechanical knee symptoms (e.g., catching or locking) indicative of clinically significant meniscal pathology
- Significant meniscal or ligament pathology based on magnetic resonance imaging
- Physical examination findings of a positive McMurray or Apley test
- Recurrent giving way of the knee Finding of a positive Lachman test Positive anterior or posterior drawer test
- Symptoms originating from the patellofemoral joint
- Avascular necrosis
- History of knee buckling or recent (within two months) knee
- injury
- Replacement of any lower extremity joint
- Use of a hinged knee brace within the past six months Current or recent past use (within two months) of oral corticosteroids
- Severe knee malalignment of more than 5 degrees from neutral
- Intra-articular injection of corticosteroids within the past 2
- months or planned for the next 12 months
  Intra-articular injection of hyaluronic acid within the past 2
- months or planned for the next 12 months
  Cognitive impairments that would limit a subject's understanding
-
-
-

Contacts/Locations

Central Contact Person: Gary Beaupre, PhD

Telephone: (650) 493-5000 Ext. 64272

Email: Gary.Beaupre@va.gov

Study Officials: Gary Beaupre, PhD Principal Investigator

VA Palo Alto Health Care System, Palo Alto, CA Locations: United States, California

VA Palo Alto Health Care System, Palo Alto, CA

Palo Alto, California, United States, 94304-1290

Contact: Contact: Gary Beaupre, PhD 650-493-5000 Ext. 64272 Gary.Beaupre@va.gov

Contact: Principal Investigator: Gary Beaupre, PhD

Stanford University, Depts: Bioengineering; Orthopaedics

Stanford, California, United States, 94305

Contact: Contact: Scott Uhlrich, MS 650-721-2547

IPDSharing

Plan to Share IPD: No

References

Citations: Links:

Available IPD/Information

Institutional Review Board – Final

eProtocol # 37721 (Final Report)
PD: Julie Ann Kolesar
Review Type: Regular
Medical

PROTOCOL
APPLICATION FORM
Human Subjects Research
Stanford University

Title : Long-Term Effectiveness of Walking Training in Patients with Knee Osteoarthritis
Closed: 01/05/2022

Title : Long-Term Effectiveness of Walking Training in Patients with Knee Osteoarthritis
Closed: 01/05/2022

Final Report Form

1. Confirm	Yes/No
a. Is this study closed to enrollment?	Y
b. Have all participants completed all research-related interventions?	Y
c. Have all the participants completed all research-related follow-up?	Y
d. Has the Stanford data analysis been completed?	Y
e. Have you confirmed with your sponsor that the study can be closed with the IRB?	Y
f. If this is a multi-site study and Stanford is the coordinating institution or the Stanfordinvestigator is the lead investigator, is the study closed at all participating sites?	

2. Number of participants enrolled since the beginning of the study.
(enrolled includes all participants who signed a consent form, whether they were later deemed ineligible)

Total consented: 276

3. Provide a summary of withdrawals from the research (both participant and investigator initiated) sincethe beginning of the study. Included the number and reasons for withdrawal.

Total withdrawals: 212

Due to COVID shutdown: 7 (unable to complete intervention due to restrictions on in-person research activity)
Investigator initiated: 198 (did not meet inclusion/exclusion criteria)
Participant initiated: 7 (dropped out due to life event or time commitment)

4. Number of participants lost to follow-up since the beginning of the study.

3 (stopped responding to email and phone)

5. If any new or unanticipated risks were identified from this study, provide a summary of the risksidentified.

None

None

6. If any participant experienced unanticipated harms or injuries, provide a summary of the harmsexperienced.

7. If any participant experienced unforeseen benefits from participation, provide a summary of the benefits.

None

8. Please provide a summary of the findings and information you learned through the study.

The purpose of our study was to evaluate the efficacy of a personalized foot progression angle (FPA) modification compared to sham gait retraining for individuals with mild-moderate medial knee osteoarthritis (OA). Our primary hypotheses were confirmed: after one year, individuals who adopted a personalized FPA modification reduced both their peak knee adduction moment (between-group difference = -0.26 %BW*ht; 95% CI: -0.39, -0.13 %BW*ht; P<.001) and medial knee pain (between-group difference = -1.2; 95% CI: -1.9, -0.5; P=.001) more than individuals who received sham gait retraining. The individuals in the intervention group also showed slowed degeneration of MRI-based estimates of cartilage microstructural health (T1rho relaxation time between-group difference= 3.74 ms; 95% CI: -6.42, -1.05 ms; P=.006). Taken together, our findings showed that personalized FPA modifications improved pain, reduced joint loading, and slowed

cartilage degeneration, demonstrating promise as an effective tool in the conservative management of medial knee osteoarthritis.

Protocol Director

Name		Degree (Program/year if student)		Position, e.g. Assistant Professor, Resident, etc.
Julie Ann Kolesar		PhD		Research Biomedical Engineer
Department VAPAHCS	153	**Phone** 650-493-5000 x67677		**E-mail** julie14@stanford.edu
CITI Training current				Y

Admin Contact

Name		Degree (Program/year if student)		Position, e.g. Assistant Professor, Resident, etc.
Julie Ann Kolesar		PhD		Research Biomedical Engineer
Department VAPAHCS	153	**Phone** 650-493-5000 x67677		**E-mail** julie14@stanford.edu
CITI Training current				Y

Investigator

Name		Degree (Program/year if student)		Position, e.g. Assistant Professor, Resident, etc.
Department		**Phone**		**E-mail**
CITI Training current				

Other Contact

Name		Degree (Program/year if student)		Position, e.g. Assistant Professor, Resident, etc.
Scott David Uhlrich		MS		PhD student
Department MechanicalEngineering	6175	**Phone** 650-721-2547		**E-mail** suhlrich@stanford.edu
CITI Training current				Y

Academic Sponsor

Name		Degree (Program/year if student)		Position, e.g. Assistant Professor, Resident, etc.
Department		**Phone**		**E-mail**
CITI Training current				

Title : Long-Term Effectiveness of Walking Training in Patients with Knee Osteoarthritis

Closed: 01/05/2022

Other Personnel

Name		Degree (Program/year if student)		Position, e.g. Assistant Professor, Resident, etc.
Garry Evan Gold		MD		Professor
Department Rad/Musculoskeletal Imaging	5488	**Phone** 650-724-0361	650-725-7296	**E-mail** gold@stanford.edu
CITI Training current				Y
Name Andrea Kate Finlay		**Degree (Program/year if student)** PhD		**Position, e.g. Assistant Professor, Resident, etc.** Instructor (Affiliated)
Department Medicine - Med/General Internal Medicine	152-MPD	**Phone** 650-493-5000 x23426		**E-mail** andrea.finlay@va.gov
CITI Training current				Y
Name Scott L Delp		**Degree (Program/year if student)** Ph.D.		**Position, e.g. Assistant Professor, Resident, etc.** Professor
Department Bioengineering	5444	**Phone** 650-723-1230	(650) 723-8544	**E-mail** delp@stanford.edu
CITI Training current				Y
Name Valentina Mazzoli		**Degree (Program/year if student)**		**Position, e.g. Assistant Professor, Resident, etc.**
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CITI Training current				Y
Name Melissa Ann Boswell		**Degree (Program/year if student)**		**Position, e.g. Assistant Professor, Resident, etc.**
Department Bioengineering		**Phone**		**E-mail** boswellm@stanford.edu
CITI Training current				Y
Name Dr. Gary Beaupre		**Degree (Program/year if student)** PhD		**Position, e.g. Assistant Professor, Resident, etc.** Professor - Consulting
Department Bioengineering		**Phone** 650-493-5000 x64272		**E-mail** gary.beaupre@va.gov

CITI Training current				Y
Name Kirsten Anne Seagers		**Degree (Program/year if student)**		**Position, e.g. Assistant Professor, Resident, etc.**
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MechanicalEngineering				kseagers@stanford.edu
CITI Training current				Y
Name Mengfei Yu		**Degree (Program/year if student)**		**Position, e.g. Assistant Professor, Resident, etc.**
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CITI Training current				Y
Name Lukasz Kidzinski		**Degree (Program/year if student)**		**Position, e.g. Assistant Professor, Resident, etc.**
Department Bioengineering	4245	**Phone**		**E-mail** kidzinsk@stanford.edu
CITI Training current				Y
Name Leyton Justin Ho		**Degree (Program/year if student)**		**Position, e.g. Assistant Professor, Resident, etc.**
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CITI Training current				Y
Name Andrew Yock		**Degree (Program/year if student)**		**Position, e.g. Assistant Professor, Resident, etc.** Research Assistant
Department Bioengineering	5444	**Phone**		**E-mail** yock@usc.edu
CITI Training current				Y
Name Andrew Ju Young Song		**Degree (Program/year if student)**		**Position, e.g. Assistant Professor, Resident, etc.**
Department Vice Provost for Undergraduate Education		**Phone**		**E-mail** ajsong@stanford.edu
CITI Training current				Y
Name Elka Rubin		**Degree (Program/year if student)**		**Position, e.g. Assistant Professor, Resident, etc.** Life Science Research Professional I
Department Rad/Musculoskeletal Imaging	5488	**Phone** (919) 932-0176		**E-mail** erubin3@stanford.edu
CITI Training current				Y

Title : Long-Term Effectiveness of Walking Training in Patients with Knee Osteoarthritis

Closed: 01/05/2022

Participant Population(s) Checklist	Yes/No
• Children (under 18)	N
• Pregnant Women and Fetuses	N
• Neonates (0 - 28 days)	N
• Abortuses	N
• Impaired Decision Making Capacity	N
• Cancer Subjects	N
• Laboratory Personnel	N
• Healthy Volunteers	N
• Students	N
• Employees	N
• Prisoners	N
• Other (i.e., any population that is not specified above)	Y
• International Participants	N

Please enter the countries separated by comma

Study Location(s) Checklist	Yes/No
• Stanford University	Y
• Clinical & Translational Research Unit (CTRU)	
• Stanford Hospital and Clinics	
• Lucile Packard Children's Hospital (LPCH)	
• VAPAHCS (Specify PI at VA)	Y

Kolesar, Julie A.

- Other (Click ADD to specify details)

General Checklist

Multi-site	Yes/No
• Is this a multi-site study? A multi-site study is generally a study that involves one or more medical or research institutions in which one site takes a lead role.(e.g., multi-site clinical trial)	N

Collaborating Institution(s)	Yes/No
• Are there any collaborating institution(s)? A collaborating institution is generally an institution that collaborates equally on a research endeavor with one or more institutions.	N

Cancer Institute	Yes/No
• Cancer-Related Studies (studies with cancer endpoints), Cancer Subjects (e.g., clinical	N

trials, behavior/prevention) or Cancer Specimens (e.g., blood, tissue, cells, body fluids witha scientific hypothesis stated in the protocol).

Clinical Trials	**Yes/No**
• Investigational drugs, biologics, reagents, or chemicals?	N
• Commercially available drugs, reagents, or other chemicals administered to subjects (even if they are not being studied)?	N
• Investigational Device / Commercial Device used off-label?	Y
• IDE Exempt Device (Commercial Device used according to label, Investigational In Vitro Device or Assay, or Consumer Preference/Modifications/Combinations of Approved Devices)	Y
• Will this study be registered on# clinicaltrials.gov? (See Stanford decision tree)	Y
• Who will register for ClinicalTrials.gov? NCT#	N

Tissues and Specimens	**Yes/No**
• Human blood, cells, tissues, or body fluids (tissues)?	N
• Tissues to be stored for future research projects?	N
• Tissues to be sent out of this institution as part of a research agreement? For guidelines, please see https://sites.stanford.edu/ico/mtas	N

Biosafety (APB)	**Yes/No**
• Are you submitting a Human Gene Transfer investigation using a biological agent or recombinant DNA vector? Please review the Administrative Panel on BioSafety website form more information.	N
• Are you submitting a Human study using biohazardous/infectious agents? If yes, refer to the Administrative Panel on BioSafety website prior to performing studies.	N
• Are you submitting a Human study using samples from subjects that are known or likely to contain biohazardous/infectious agents? If yes, refer to the Administrative Panel on BioSafety website prior to performing studies.	N

Human Embryos or Stem Cells	**Yes/No**
• Human Embryos or Gametes?	N
• Human Stem Cells (including hESC, iPSC, cancer stem cells, progenitor cells)	N

Veterans Affairs (VA)	**Yes/No**
• The research recruits participants at the Veterans Affairs Palo Alto Health Care	Y

VAPAHCS).

- The research involves the use of VAPAHCS non-public information to identify or contact human research participants or prospective subjects or to use such data for research purposes. Y
- The research is sponsored (i.e., funded) by VAPAHCS. Y
- The research is conducted by or under the direction of any employee or agent of VAPAHCS (full-time, part-time, intermittent, consultant, without compensation (WOC), on-station fee-basis, on-station contract, or on-station sharing agreement basis) inconnection with her/his VAPAHCS responsibilities. Y
- The research is conducted using any property or facility of VAPAHCS. Y

Equipment **Yes/No**

- Use of Patient related equipment? If Yes, equipment must meet the standards established by Hospital Instrumentation and Electrical Safety Committee (650-725-5000) Y
- Medical equipment used for human patients/subjects also used on animals? Y
- Radioisotopes/radiation-producing machines, even if standard of care? http://www.stanford.edu/dept/EHS/prod/researchlab/radlaser/Human_use_guide.pdf More Info Y

Payment **Yes/No**

- Subjects will be paid/reimbursed for participation? See payment considerations. Y

Funding **Yes/No**

- Training Grant? N
- Program Project Grant? N
- Federally Sponsored Project? Y
- https://doresearch.stanford.edu/policies/research-policy-handbook/ N
- definitions-and-types-agreements/specialized-categories-sponsored- Industry Sponsored Clinical Trial?

Funding

Funding - Grants/Contracts

Funding Administered By :	VA	**SPO # (if available) :**	
Grant # (if available) :	1I01RX001811-01A2	**Funded By (include pending) :**	Department of Veterans Affairs
Principal Investigator :	Kolesar, Julie		

Grant/Contract Title if different from Protocol Title :

Personalized Gait Training with Feedback to Reduce Knee Pain from Osteoarthritis

Y For Federal projects, are contents of this protocol consistent with the Federal proposal?

Is this protocol under a MPP?

Funding - Fellowships

Gift Funding

Dept. Funding

Other Funding

Resources :

a) Qualified staff.

Please state and justify the number and qualifications of your study staff.

Julie Kolesar, PhD
Dr. Kolesar is the Principal Investigator, a Research Biomedical Engineer at VAPAHCS, and a Visiting Scholar in the Stanford Human Performance Lab. She has extensive experience with human subject experiments and in the collection and analysis of biomechanical data. Dr. Kolesar will be responsible for overall project management and for coordinating the work outlined in the study. Dr. Kolesar will assure that all project personnel are appropriately trained in the techniques being used and all required safety measures are followed. Furthermore, she will be responsible for ensuring that research goals are met in a timely manner with scientific integrity, that work is done within the approved budget, and that all aspects of the research study are done in accordance with VA regulations. Dr. Kolesar will also assist with data collection and analysis for the project.

Gary Beaupre, PhD
Dr. Beaupre is a VA Research Career Scientist who has more than thirty years of experience in multiple research areas within the field of orthopaedic biomechanics and is a recognized international expert. Dr. Beaupre will provide assistance on overall project management, particularly as related to VA requirements and regulations.

Garry Gold, MD
Dr. Gold is a clinical musculoskeletal radiologist and researcher in magnetic resonance imaging (MRI) of osteoarthritis and musculoskeletal disease. He is a professor in the Department of Radiology at Stanford and a member of the VA Department of Radiology. Dr. Gold has nearly twenty years of experience designing and testing imaging protocols for studies of cartilage and joint disease and he leads several NIH-funded projects in this area. He will provide expertise on all imaging aspects of the project. He has substantial prior experience in projects with human subjects, including recruiting, consenting, data collection, analysis and data security.

Andrea Finlay, PhD
Dr. Finlay is a Research Health Scientist at the Center for Innovation to Implementation at the VA Palo Health Care System. Dr. Finlay has extensive experience in statistical design and analysis, with specific expertise in intent-to-treat analyses. Dr. Finlay will provide consulting assistance on any statistical issues that arise and she will contribute to the development of all presentations, reports, and publications derived from the analyses.

Scott Delp, PhD
Dr. Delp is the James H. Clark Professor of Bioengineering at Stanford University. Dr. Delp is an

internationally recognized expert in neuro-musculo-skeletal biomechanics. Dr. Delp is the Co-Director of the Stanford Human Performance Laboratory (HPL) and one of the original team members who contributed to the preliminary studies of gait retraining with real-time haptic feedback which served as the foundation for the current study. He will serve in a comparable role during the planned project.

Scott Uhlrich, MS
Mr. Uhlrich is a Stanford PhD student who has extensive experience in motion capture and gait retraining. Mr. Uhlrich has experience in the collection of biomechanical data and analysis. He will assist in the collection of biomechanical data for the project.

Valentina Mazzoli, PhD
Dr. Mazzoli is a postdoctoral fellow in the Radiology department of Stanford University. She has extensive experience with imaging protocols and processing, and will assist with collection and analysis of MRI images.

Madeleine Berkson, BS
Ms. Berkson is a recent graduate of the Stanford University Mechanical Engineering department. She will be assisting with recruitment, consenting, data collection and analysis for the project.

Evangeline Vijayakumar
Ms. Vijayakumar has experience coordinating clinical trials and recruiting subjects for participation. She will be in charge of recruiting and consenting research subjects for this study.

a) Training.

Describe the training you will provide to ensure that all persons assisting with the research areinformed about the protocol and their research-related duties and functions.

All the personnel involved in the protocol are fully aware of the inclusion/exclusion criteria, the design, and the data being acquired. Each member of the research staff is experienced with human subjects research and is fully aware of HIPAA compliance and rules. The staff will read the protocol and will be trained regarding the protocol and their specific duties and functions by Dr. Kolesar. Staff will complete all trainings on proper research involving human subjects and on maintaining data security and subject confidentiality.

b) Facilities.

Please describe and justify.

Human Performance Laboratory, Stanford University
The Human Performance Laboratory (HPL) at Stanford University is a 2,500 square foot Core facility that supports interdisciplinary research in the fields of biomechanics, biomedical engineering, exercise physiology, orthopedics and rehabilitation. The HPL has the unique capability of being able to perform motion capture while individuals walk at constant speed, while continuously and simultaneously acquiringground reaction forces from two independent force plates that are integrated into an instrumented split-belttreadmill system. Motion capture during treadmill walking will be accomplished with a 10-camera
three-dimensional motion capture system.
Gait Laboratory at VAPAHCS
This is a motion capture laboratory located in Building T6 at the VAPAHCS. The Lab includes a ten camera Qualisys motion capture system along with multiple force plates, and is dedicated to the analysis of human movement. The Lab also includes office space and computer facilities.
Lucas Center, Stanford University
This large imaging research center has 3T scanners that are available for research imaging purposes and are configured to perform the advanced scans that will be performed in this study.

Radiology at VAPAHCS
The radiology department at the VAPAHCS has both MRI scanners and X-ray facilities and may be used to obtain lower limb radiographs and MRIs for the study.

Orthopaedic & Rheumatology Clinics at VAPAHCS and Stanford
Initial identification of potential subjects will be done by clinicians at VAPAHCS and Stanford. Prospective subjects will be instructed to contact a member of our research team for additional information about the project.

c) Sufficient time.

Explain whether you will have sufficient time to conduct and complete the research. Include how much

We propose to include 104 subjects over the course of 4 years who will complete a 52-week intervention. We expect to screen approximately 200 subjects in order to wind up with 104 subjects who complete the intervention. Our team has the experience and the time commitment to ensure that the project remains on track to be completed within the proposed time frame.

time is required.

d) Access to target population.

Explain and justify whether you will have access to a population that will allow recruitment of the

VA and Stanford Orthopaedic and Rheumatology clinicians will identify potential subjects meeting the inclusion and exclusion criteria at the time of their clinic visit. Departmental clinicians will notify potential subjects about the study and ask permission to have a clinical coordinator contact him/her with more information. If permission is granted, the clinical coordinator will follow-up in person at the clinic or by phone to answer any questions and to arrange for consenting. Based on discussions with the clinicians who staff the clinics in question we anticipate no problem recruiting the required number of subjects over the course of 4 years.

required number of participants.

e) Access to resources if needed as a consequence of the research.

State whether you have medical or psychological resources available that participants might require asa consequence of the research when applicable. Please describe these resources.

We do not foresee any medical or psychological consequences as our research protocol poses minimal risks to our subjects. However, in the event of an unexpected emergency, medical or psychological, resources that participants might require are located at VA Palo Alto Health Care System and at the Stanford University Hospital and Clinics.

f) Lead Investigator or Coordinating Institution in Multi-site Study.

Please explain (i) your role in coordinating the studies, (ii) procedures for routine communication with other sites, (iii) documentation of routine communications with other sites, (iv) planned management of communication of adverse outcomes, unexpected problems involving risk to participants or others,

protocol modifications or interim findings.

1. Purpose

a) In layperson's language state the purpose of the study in 3-5 sentences.

Nearly one out of every two Americans will develop knee
osteoarthritis by age 85. While a
daily walking regimen is known to reduce pain from knee arthritis,

gait retraining
combined with walking has the potential to reduce excessive forces
on the medial
compartment of the knee, thereby slowing disease progression. Our
study will determine if
gait training provides an additional benefit from walking that is
long-lasting and leads to a
greater pain reduction than walking alone.

b) State what the Investigator(s) hope to learn from the study. Include an assessment of the importance of this new knowledge.

The information obtained during this study will help advance
scientific and clinical
understanding of the effects of biomechanics on the progression and
novel conservative
treatment of knee osteoarthritis.

c) Explain why human subjects must be used for this project. (**i.e. purpose of study is to test efficacy of investigational device in individuals with specific condition; purpose of study is to examine specific**

The only way to test the hypothesis posed is by using human
subjects, as the hypotheses of
our study are directly related to the biomechanics of human
locomotion and the benefits of
walking as a conservative treatment for knee osteoarthritis.
Animal models are not possible
for the testing of our hypotheses.

behavioral traits in humans in classroom or other environment)

2. Study Procedures

a) Please SUMMARIZE the research procedures, screening through closeout, which the human subject will undergo. Refer to sections in the protocol attached in section 16, BUT do not copy the clinical protocol. Be

The following lists all major research procedures. Each procedure
is done for research;
none is done as part of standard of care.

Recruitment, Screening, Randomization of Subjects: VA and Stanford
Orthopaedic and
Rheumatology clinicians will initially identify potential
participants, who will then talk or
meet with study investigators. Potential participants will be
block randomized into one of
two intervention arms by a study investigator (the differences in
intervention arms can bee seen in "Haptic Feedback" Section
below).
Potential participants will be screened for
eligibility and consented by a study investigator.

Knee MRI: Subjects will have a knee MRI scans at baseline and week
52. Longer-term, optional, follow-up MRI scans may be obtained at
24,
36, and 48 months.

clear on what is to be done for research and what is part of standard of care.

Knee Radiographs: For subjects who do not have current clinicalknee radiographs, research knee radiographs will be obtained at baseline. Follow-upresearch radiographs will be obtained at week 52. Optional radiographs may be taken at24, 36, and 48 months.

Gait Analysis: Subjects will have gait analysis at weeks 1, 7, 11,25, 39 and 52. During those sessions we will record motion data, ground contact force data,and possibly muscle activation (EMG).

Gait Training: Subjects will undergo gait training using real-timehaptic feedback (see description below) while walking on a treadmill. Gait trainingwill take place during weeks 2, 3, 4, 5, 6, and 7. Refresher training may take place during weeks 11, 25 and 39. Subjects will either be trained for foot progression angleconsistency or foot progression angle modification. If subjects are uncomfortable with treadmill walking, they may come to the Human Performance Lab to practice walking on the treadmill before they begin gait training.

Haptic Feedback: Haptic feedback will be administered through aminiature, wearable vibration motor or tactor. The tactor is attached to the skin withVelcro or human-safe adhesive tape and vibrates to give users feedback on a step-by-step basis while walking. The vibration motor is similar to the vibration motor inside mostcell phones. Haptic feedback will be used to give real time feedback to participants about the way that they walk. The only differencebetween the intervention arms is the foot angle that they are givenfeedback to achieve.

Pedometer & Smart Shoe Monitoring: Subjects will use a pedometerand use smart shoes during weeks 1, 7, 11, 25, 39 and 52.

Knee health questionnaire & pain score: Subjects will complete theKOOS clinical questionnaire and asses their knee pain using a standardized painscale during weeks 1, 7, 11, 25, 39 and 52.

Home and Community-Based Walking: Subjects will walk a minimum of 20

minutes per day throughout the 52-week intervention. Subjects will maintain daily walking activity logs in which they record their estimated number of walking minutes per day.

b) Explain how the above research procedures are the least risky that can be performed consistent with sound research design.

The research protocol poses minimal risk to patients. All research procedures are essential for testing the hypotheses in the study and are consistent with sound research design.
Risk from radiographs: The study-related radiographs will result in an additional effective dose equivalent of 8.63 days of background radiation which is negligible.
Risks from MRI: MRI is non-invasive and non-ionizing. All subjects will undergo screening for metal in the body prior to MRI scanning. If the screening indicates that potentially dangerous metal may be present, the subject will be excluded. The MRI poses no more risk than that of a standard clinical MRI exam with FDA-approved sequences.
Rsks from gait analysis: Subjects will be asked to walk in a well-lit gait lab while wearing reflective markers. The collection of 3D motion capture data, EMG data, and ground reaction forces are all non-invasive and pose minimal risk to the participants. There is no more risk to the subjects beyond the normal risks associated with walking.
Risks from treadmill walking and gait training: While there is a minor risk of injury while walking on a treadmill, the likelihood and severity of an injury is not greater than while walking on a treadmill in a gym. The treadmill has a safety handrail to reduce the risk of falling and the treadmill has an emergency stop button. Subjects who do not feel comfortable with treadmill walking may practice as long as needed to feel comfortable with close supervision by research staff. The haptic devices used for gait training vibrate on the skin like a cell phone vibrates and thus provide little to no chance of injury.

Risk from pain scoring: There is no risk to subjects from filling out a standardized pain scale to assess knee pain.

c)

Risks from questionnaire: There is no risk to subjects from filling out the clinical knee questionnaire.

Risk from pedometer: There is no risk to subjects from using a pedometer to record steps while walking under free-living conditions.

Risk from use of Smart Shoes: Wearing the smart shoes poses no greater risk to the subjects than wearing any new pair of athletic shoes. There is the minor risk of developing a blister if they don't fit properly, but we will have an assortment of sizes to offer to provide an acceptable fit. Another minor risk is that the insole will have an arch that is not comfortable, but we will have an assortment of after-market insoles (Superfeet) in different sizes and styles if a subject feels the default arch is uncomfortable.

Risk from additional walking under free-living conditions: There is no more risk to the subjects beyond the normal risks associated with walking under free-living conditions.

d) State if deception will be used. If so, provide the rationale and describe debriefing procedures. Since you will not be fully informing the participant in your consent process and form, complete an alteration of consent (in section 13). Submit a debriefing script (in section 16).

Deception will not be used.

e) State if audio or video recording will occur. Describe what will become of the recording after use, e.g.,

Images and video recordings may be made while subjects perform research-related tasks in order to assist with subsequent data analysis. Images and video recordings may also be used at scientific meetings. Before any public use, images or videos will be fully de-identified, including masking of the subjects' faces. Images or video stored on portable media (e.g., USB flash drive, memory card, CD, DVD, tape) will be kept in a locked cabinet in a locked room accessible only to approved members of the research staff. Images and videos that may be saved indefinitely for scientific presentation will be kept on a secure server behind the VA firewall accessible only to approved members of the research staff.

shown at scientific meetings, erased. Describe the final disposition of the recordings.

A key objective of the study is assessing the persistence at 12 months (52 weeks) of a benefit from a regular walking regimen, both in a group thatmaintains their natural and consistent foot progression angle, and in a group that adopts an altered foot progression angle. Based on previous studies, we expect to see a benefit inboth groups at shorter time points, however it is not know if those benefit remain at 12 months. By definition that assessment requires evaluating the results at 12 months.

Given the lack of data on MRI detectable changes to cartilage over a 12-month time frame for this type of walking-based intervention, it is possible thatwe will not be able to detect early changes in cartilage thickness or physiological properties via MRI. Such changes will be more easily detected at longer assessment time points. We willinclude a provision in the informed consent that will allow us to contact subjects after they complete their 12-month participation. We will attempt to rescan subjects enrolled duringyear one at their 24 and 36-month time points. All subjects initially enrolled during year two will be asked to have repeat scans at their 24-month time point. In this way, we may beable to collect longer term MRI data for up to two-thirds of the original cohort. For subjects enrolled during year 3 it may not be possible to scan them past the 12-month time point dueto the duration of study funding and staffing after the end of funding. Nevertheless, we

f)

g) Describe alternative procedures or courses of treatment, if any, that might be advantageous to the participant. Describe potential risks and benefits associated with these. Any standard treatment that is being withheld must be disclosed in the consent process and form. (i.e. standard-of-care drug, different

No standard treatment is being proposed or withheld.

interventional procedure, no procedure or treatment, palliative care, other research studies).

h) Will it be possible to continue the more (most) appropriate therapy for the participant(s) after the conclusion of the study?

Yes. If we find convincing evidence for the long-term benefit of walking with either one's natural foot progression angle or with an altered foot progression angle, then subjects will be free to continue that practice after the conclusion of the study.

i) Study Endpoint. What are the guidelines or end points by which you can evaluate the different treatments (i.e. study drug, device, procedure) during the study? If one proves to be clearly more effective than another (or others) during the course of a study, will the study be terminated before the projected total participant population has been enrolled? When will the study end if no important differences are detected?

may be able to collect
longer
term MRI data for up to two-thirds of the original cohort.

3. Background

a) Describe past experimental and/or clinical findings leading to the formulation of the study.

Members of our research team previously demonstrated the
effectiveness of real-time,
haptic, gait retraining for individuals with knee OA in a six-week
pilot study that was
reported in the Journal of Orthopaedic Research (Shull et al., J
Orthop Res 31:1020-5,
2013).
Participating in a walking program for reducing pain for
individuals with OA has also been
shown to reduce knee pain in both 8-week (Kovar et al. 1992) and
12-week (Minor et al.,
1989; Peloquin et al.,1999) studies.

These studies lead us to believe that by maintaining one's natural
foot progression angle,
or by optimally modifying one's foot progression angle, when
combined with additional
daily walking, will have a short-term benefit and the goal of our
study is to test whether
that
benefit will still be present at the end of a 52-week
intervention.

b) Describe any animal experimentation and findings leading to the formulation of the study.

None.

4. Radioisotopes or Radiation Machines

a) List all standard of care procedures using ionizing radiation (radiation dose received by a subject that is considered part of their normal medical care). List all research procedures using ionizing radiation (procedures performed due to participation in this study that is not considered part of their normal medical care). List each potential procedure in the sequence that it would normally occur during theentire study. More Info

Identify Week/Month of study	Name of Exam	Identify if SOC or Research
Week 0 (if needed)	Weight-Bearing Knee X-rays	Research
Week 52	Weight-Bearing Knee X-rays	Research
Month 24	Optional Weight-Bearing KneeX-rays	Research
Month 36	Optional Weight-Bearing KneeX-rays	Research
Month 48	Optional Weight-Bearing Knee X-rays	Research

b) For research radioisotope projects, provide the following radiation-related information:Identify the radionuclide(s) and chemical form(s).

N/A

For the typical subject, provide the total number of times the radioisotope and activity will be administered (mCi) and the route of administration.

N/A

If not FDA approved provide dosimetry information and reference the source documents (package insert, MIRD calculation, peer reviewed literature).

N/A

c) For research radiation machine projects, provide the following diagnostic procedures:For well-established radiographic procedures describe the exam.

Weight bearing x-rays of the knee will be taken at five time points for each subject to determine the condition of the cartilage and bone in the knee. There will be 5 radiographs taken at week 0 and 4 radiographs per visit thereafter. An AP, lateral, notch, and sunrise view will be taken at each radiography visit. At Week 0, a 36 inch, full leg view to also assess mechanical alignment of the lower limbs.

For the typical subject, identify the total number of times each will be performed on a singleresearch

Up to two times per subject for the minimum 52 week participation. If subjects choose to partake in the 24, 36, and 48 month optional imaging sessions, the knee x-rays would be performed a maximum of 5 times.

subject.

For each radiographic procedure, provide the setup and technique sufficient to permit researchsubject dose modeling. The chief technologist can usually provide this information.

With the exception of the 36" AP radiograph at week 0 (0.049 millisievert), each radiograph view involves an effective radiation dose of 0.001 millisieverts, making for a total radiation exposure of 0.069 millisieverts (first exam: 0.053 millisieverts (0.049+4*0.001) + 4 radiographs * 4 exams * 0.001 millisieverts = 0.069 millisieverts) which is equivalent to 8.63 days of background radiation over the 4 year span of the study.

http://www.radiologyinfo.org/en/info.cfm?pg=safety-xray (accessed 07/19/2016)

Kloth et. al, 2014. "Quality-controlled dose reduction of full-leg radiography in patients with knee malalignment," Skeletal Radiology 44(3), pp. 423-429.

For radiographic procedures not well-established, provide FDA status of the machine, andinformation

N/A

sufficient to permit research subject dose modeling.

d) For research radiation machine projects, provide the following therapeutic procedures:

For a well-established therapeutic procedure, identify the area treated, dose per fraction and number of fractions. State whether the therapeutic procedure is being performed as a normal part of clinical management for the research participants's medical condition or whether it is being performed because

N/A

the research participant is participating in this project.

For a therapeutic procedure that is not well-established, provide FDA status of the machine, basisfor dosimetry, area treated, dose per fraction and number of fractions.

N/A

1. Devices

a) Please list in the table below all Investigational Devices (including Commercial Devices used off-label) tobe used on participants.

5. 1 Device Name : Smart Shoes Describe the device to be used.

Smart Shoes are standard athletic shoes with an encapsulated sensor embedded within the sole that measures and records the direction the toes point when walking.

Manufacturer : Custom built

Risk : Non-significant

Y I confirm the above are true.

Rationale for the device being non-significant risk:

Wearing the smart shoes poses no greater risk than wearing any new pair of athletic shoes. There is the minor risk of developing a blister if they don't fit properly, but we will have an assortment of sizes to offer to facilitate an acceptable fit. Another minor risk is that the insole will have an arch that is not comfortable, but we will have an assortment of after-market insoles (Superfeet) in different sizes and styles if a subject feels the default arch is uncomfortable. If no size of shoe or insole proves to be acceptably comfortable, the subject will not be required to wear the smart shoes.

Sponsor of Project

Indicate who is responsible for submitting safety reports to the FDA:

Y The sponsor is a non-STANFORD investigator or group.

Ordering, Storage and Control

To prevent the device being used by a person other than the investigator, and in someone other than a research participant: Confirm that the device will be handled according to the SHC/LPCH policy for Investigational New Devices or as appropriate. If no, please provide an explanation. :

Y Confirm?

5. 2 Device Name : GE Signa Describe the device to be used.

MRI scanner

Manufacturer : GE Healthcare

Risk : Non-significant

Y I confirm the above are true.

Rationale for the device being non-significant risk:

Some of the RF coils, imaging accessories and equipment, and imaging software used to scan subjectsat the Lucas Center are not FDA-approved.

The MR research being conducted requires highlyspecialized equipment and

imaging software that does not exist in the clinical MR market so it is designed and manufactured by researchers at the Lucas Center and other hardware companies. Although some of the imaging software and equipment are not FDA approved, they have been tested for safety and are very similar to what is used regularly in clinical MR examinations. The MR personnel are highly trained in the set-up, utilization, and monitoring of this equipment.

Sponsor of Project

Indicate who is responsible for submitting safety reports to the FDA:

Y The sponsor is a non-STANFORD investigator or group.

Ordering, Storage and Control

To prevent the device being used by a person other than the investigator, and in someone other than a research participant: Confirm that the device will be handled according to the SHC/LPCH policy for Investigational New Devices or as appropriate. If no, please provide an explanation. :

Y Confirm?

b) Please list in the table below all IDE Exempt Devices (Commercial Device used according to label, Investigational In Vitro Device or Assay, or Consumer Preference/Modifications/Combinations ofApproved Devices) to be used on participants.

5. 1 Device Name : C2 TactorDescribe the device to be used.

Wearable vibration device

Manufacturer Engineering Acoustics Inc. (EAI)

IDE Exemption

Y **This is a legally marketed device being used in accordance with its labeling.**

6. Drugs, Reagents, or Chemicals and Devices

a) Please list in the table below all investigational drugs, reagents or chemicals to be administered to participants.

b) Please list in the table below all commercial drugs, reagents or chemicals to be administered to participants.

7. Medical Equipment for Human Subjects and Laboratory Animals

If medical equipment used for human patients/participants is also used on animals, describe such equipment and disinfection procedures.

The bed/table and accessories that are used for the animals is different than the table humans use. Physiologic

monitoring equipment is cleaned with a commercial disinfectant such as Roccal, Conflick, Sani-Wipes, or a 10% Bleach solution. All RF coils and positioning accessories are wrapped in plastic wrap or plastic bags for use with animals. Everything, even if it is animal use only, is cleaned with the above disinfectants after every use even if they are wrapped in plastic. The Lucas Center is checked yearly by several groups at Stanford who approve animal research in human systems: Stanford Health & Safety. We are reviewed by: Stanford APLAC panel; USDA; NIH; and Aaalac.

8. Participant Population

a) State the following: (i) the number of participants expected to be enrolled at Stanford-affiliated site(s); (ii)the total number of participants expected to enroll at all sites; (iii) the type of participants (i.e. students, patients with certain cancer, patients with certain cardiac condition) and the reasons forusing uch participants.

(i) 400 subjects expected to be screened/consented and 100 expected to be enrolled.
(ii) 400 subjects expected to be screened/consented and 100 expected to be enrolled.
(iii) Subjects will have isolated, medial compartment, osteoarthritis of the knee with a Kellgren-Lawrence grade of I, II, or III, of at least six months duration. These subjects are targeted because they have the best potential to benefit from a novel conservative treatment that involves increasing their habitual walking activity.

b) State the age range, gender, and ethnic background of the participant population being recruited.

Participants aged 18 and over will be recruited regardless of gender, race, and ethnic background.

c) State the number and rationale for involvement of potentially vulnerable subjects in the study (including children, pregnant women, economically and educationally disadvantaged, decisionally impaired, homeless people, employees and students). Specify the measures being taken to minimize the risks and the chance of harm to the potentially vulnerable subjects and the additional safeguards that

N/A

have been included in the protocol to protect their rights and welfare.

d) If women, minorities, or children are not included, a clear compelling rationale must be provided (e.g., disease does not occur in children, drug or device would interfere with normal growth and development, etc.).

Our inclusion criteria specifically allows for the inclusion of women and minorities. Children will not be included since the study is funded by the Department of Veterans Affairs, which does not conduct research using children. In addition, children do not typically develop osteoarthritis.

e) State the number, if any, of participants who are laboratory personnel, employees, and/or students. They should render the same written informed consent. If payment is allowed, they should also receiveit.

None

Please see Stanford University policy.

f) State the number, if any, of participants who are healthy volunteers. Provide rationale for the inclusion of healthy volunteers in this study. Specify any risks to which participants may possibly be exposed. Specify the measures being taken to minimize the risks and the chance of harm to the volunteers and the additional safeguards that have been included in the protocol to protect their rightsand welfare.

No participants will be healthy volunteers.

g) How will you identify and recruit potential participants about the research study? (E.g., by: Honest Broker or other https://researchcompliance.stanford.edu/participantengagement Research Participation services; chart review; treating physician; ads). All final or revised recruitment materials, flyers, etc. must be submitted to the IRB for review and approval before use. You may notcontact potential participants prior to IRB approval. See Advertisements: Appropriate Language for

Recruitment Material.

Subjects (veterans and non-veterans) will first learn about the existence (but not specific study details) of the VA study of a new conservative treatment for medial compartment knee OA from a variety of sources, including word-of-mouth, their health care provider(s) at VA, or from other Bay Area clinicians (who are aware of the existence of the study via word-of-mouth), and posted flyers. We will also consider advertising via newspapers and the internet to achieve our recruitment targets. These advertisements will use wording and images from flyers and text attached in section 16. Informational audio and visual material will be used for recruitment as approved by the IRB.

Potential research subjects will be identified from searches of electronic medical records (EPIC at Stanford Hospital and CPRS at the VA). Individuals who fit our criterion will be mailed an information letter that is attached in section 16.

h) Inclusion and Exclusion Criteria.Identify inclusion criteria.

- Diagnosed with isolated, medial compartment knee OA of at least six months duration
- Kellgren-Lawrence grade of I, II, or III
- Age greater than 18 years at the time of enrollment
- Ability to give informed consent
- Knee pain more than three days per week on average
- Average knee pain in medial compartment between 3 and 9 on a 11-point numerical rating scale, and greater than pain in other compartments
- Ambulatory without aids
- Able to walk for at least 25 consecutive minutes
- Able to walk on treadmill safely at 0.7 m/s or faster
- Able to reduce the prominent peak of the knee adduction moment by changing foot progression angle
- Inclusion is open to both genders and all ethnic and racial groups

- Body mass index equal to or greater than 35
- Pregnancy
- Plans for knee replacement within the next 12 months
- Contraindications to MRI
- Nerve or musculoskeletal disease associated with walking difficulty
- Narcotic pain medication usage
- History of rheumatoid arthritis or autoimmune disease
- An episode of gout or pseudogout in the knee in the past year
- History of neuropathic arthropathy, infectious disease, or other major systemic disease
- Current or recent past use (within two months) of oral corticosteroids
- Cognitive impairments that would limit a subject's understanding
- Expecting a significant change in activity level or weight within the next 12 months.
- Regularly participates in high impact activities such as running, soccer, basketball, etc.
- Unable to perform the 3rd stage of the 4 stage balance test. This stage involves holding tandem stance for 10 seconds.

The following criteria apply only to the affected osteoarthritic limb:
- History of symptomatic arthritis in lower limb joints other than the knees that is more severe than knee arthritis
- Replacement of any lower extremity joint
- Lateral tibiofemoral joint space width less than medial
- Recurrent giving way of the knee
- Symptoms arising primarily from a meniscal or ligament pathology or other structure not directly related to osteoarthritis as identified by physical exam, health record, or MRI.
- Symptoms originating primarily from the patellofemoral joint

Identify exclusion criteria.

- Avascular necrosis
- Recent (within two months) knee injury or surgery
- Planned use of hinged knee brace in next 12 months
- Severe knee malalignment of more than 10 degrees from neutral
- Intra-articular injection within the past 2 months or planned for the next 12 months

i) Describe your screening procedures, including how qualifying laboratory values will be obtained. Ifyou are collecting personal health information prior to enrollment (e.g., telephone screening), pleaserequest a waiver of authorization for recruitment (in section 15).

Potential participants will initially be identified by VA and Stanford Orthopedic and Rheumatology clinicians. These clinicians will be familiar with the study's inclusion and exclusion criteria. Subsequent contact with potential participants by a study team member will confirm whether they meet the inclusion and exclusion criteria and to obtain contact information.

j) Describe how you will be cognizant of other protocols in which participants might be enrolled. Please

Participants will be asked if they are enrolled in any other studies. Due to the minimal risk associated with this study, we do not see an additional risk to the participant enrolling in this study, even if he/she is enrolled in another study. However, we will not enroll subjects who are already enrolled in another study that involves a treatment for arthritis.

explain if participants will be enrolled in more than one study.

k) Payment/reimbursement. Explain the amount and schedule of payment or reimbursement, if any, that will be paid for participation in the study. Substantiate that proposed payments are reasonable and commensurate with the expected contributions of participants and that they do not constitute undue pressure on participants to volunteer for the research study. Include provisions for prorating payment. See payment considerations

Subjects will receive nominal payments of $100 after their week 7, week 25 and week 52 visits. In addition they will receive a $50 completion bonus after their week 52 visit. This translates to less than $32 per visit.

After 52-weeks of participation subjects will also be offered an Omron pedometer to keep. The pedometer has a retail value of approximately $25.

l) Costs. Please explain any costs that will be charged to the participant.

None

m) Estimate the probable duration of the entire study. Also estimate the total time per participant for: (i) screening of participant; (ii) active participation in study; (iii) analysis of participant data.

The entire study is expected to be completed in 8 years including time for recruitment, data collection, follow-up, and data processing following IRB approval.

(i) Screening and consenting of each participants is expected to take 1.0 to 1.5 hours.

(ii) Active participation is expected to take approximately 20 hours over a total of 11 laboratory visits. Most visit times will take between 15 minutes and 1.25 hours. The 52 week visit will require 4 hours. In addition to laboratory visits, all subjects are expected to increase their habitual walking activity over the entire 52-week intervention. It will be optional for subjects to receive follow-up x-rays and MRI scans at 24, 36, and 48 months. These visits will take 2 hours each and would increase their total participation time to 26 hours.

(iii) Analysis of data for each participant will require several days (participant not required to be present). Years 5-8 will be dedicated to follow-up MRI and x-ray visits, data synthesis, abstract, manuscript, and grant writing.

5. Risks

a) For the following categories include a scientific estimate of the frequency, severity, and reversibility of potentialrisks. Wherever possible, include statistical incidence of complications and the mortality rate of proposed procedures. Where there has been insufficient time to accumulate significant data on risk, a statement to this effect should be included. (In describing these risks in the consent form to the participant it is helpful to use comparisons which are meaningful to persons unfamiliar with medical terminology.)

The risks of the Investigational devices.

MRI: We will use some non-standard MRI sequences and coils; all will comply with FDA guidelines for safety and radio frequency power deposition. There are minimal risks associated with MRI including dizziness and nausea, heating and reddening of tattoos, heating of cables, claustrophobic sensations, and muscle twitching. If the participant reports any of these issues, the scan will be stopped. An additional risk of MRI is the strong magnet. Participants will be thoroughly screen prior to the scan to ensure they do not have any ferromagnetic materials in or on their person. None of the aforementioned risks are unique to the investigational nature of our sequences and coils, rather are a risk to all MRI procedures, investigational or clinical.

Smart Shoes: Wearing the smart shoes poses no greater risk to the subjects than wearing any new pair of athletic shoes. The "smart" component is a 2" x 1.5" x 0.5" thick insert that is encapsulated and embedded within the sole of the shoe. With the insoles inserted the shoes are indistinguishable from standard athletic shoes. There is a minor risk of developing a blister if the shoes don't fit properly, but we will have an assortment of sizes to offer subjects in order to provide an acceptable fit. Another minor risk is that the standard shoe insole will have an arch that is not comfortable, but we will have an assortment of after-market insoles (Superfeet) in different sizes and styles if a subject feels the default arch is uncomfortable.

The risks of the Investigational drugs. Information about risks can often be found in the Investigator's brochure.

N/A

The risks of the Commercially available drugs, reagents or chemicals. Information about risks canoften be found in the package insert.

The risks of the Procedures to be performed. Include all investigational, non-investigational andnon-invasive procedures (e.g., surgery, blood draws, treadmill tests).

N/A

Risk from radiographs: The study-related radiographs will result in an additional effective dose equivalent of 9.13 days of background radiation. This is a negligible amount.
Risks from MRI: MRI is non-invasive and non-ionizing. All subjects will undergo screening for metal in the body prior to MRI scanning. If the screening indicates that potentially dangerous metal may be present, the subject will be excluded. The MRI poses no more risk than that of a standard clinical MRI exam with FDA-approved sequences.
Risks from gait analysis & EMG: Subjects will be asked to walk in a well-lit gait lab while wearing reflective markers. There is no more risk to the subjects beyond the normal risks associated with walking. The application of the surface EMG electrodes might cause some skin irritation as the surface of the skin is prepared prior to the electrode placement with alcohol wipes and the electrode is adhered to the skin using double-sided tape. The tape is hypoallergenic to reduce the risk of skin irritation. Likewise, the application of reflective markers poses a similar risk of skin irritation as it uses the same double-sided tape to adhere the marker to the skin.
Risks from treadmill walking: While there is a minor risk of injury while walking on a treadmill, the likelihood and severity of an injury is not greater than while walking on a treadmill in a gym. The treadmill has a safety hand rail to reduce the risk of falling and the treadmill has an emergency stop button. During their first visit, subjects physical fitness to walk on the treadmill will be assessed.

Risk from haptic feedback: The haptic device or tactor is designed to be incapable of causing an injury. The tactor is a small device, about the size of a quarter dollar in diameter, and 1/4 inch thick. It is taped to the skin or held with a Velco strap. Removing the tape might cause some momentary discomfort. During use, the tactor creates a buzzing feeling that is attention getting, but not uncomfortable.
Risk from pain scoring: There is no risk to subjects from filling out a standardized rating scale to assess knee pain.
Risks from questionnaire: There is no risk to subjects from filling out the clinical knee questionnaire.
Risk from pedometer: There is no risk to subjects from using a pedometer to record steps while walking under free-living conditions.
Risk from use of Smart Shoes: Wearing the smart shoes poses no greater risk to the subjects than wearing any new pair of athletic shoes. There is the minor risk of developing a blister if they don't fit properly, but we will have an assortment of sizes to offer to provide an acceptable fit. Another minor risk is that the insole will have an arch that is not comfortable, but we will have an assortment of after-market insoles (Superfeet) in different sizes and styles if a subject feels the default arch is uncomfortable.
Risk from additional walking under free-living conditions: There is no more risk to the subjects beyond the normal risks associated with walking under free-living conditions.

The risks of the Radioisotopes/radiation-producing machines (e.g., X-rays, CT scans, fluoroscopy) and associated risks.

This research study involves exposure to radiation from knee x-ray that is not necessary for your medical care and is for research purposes only. The additional amount of radiation is approximately equal to 9.13 days of radiation exposure from natural sources like the sun, ground and water. This amount of radiation involves minimal risk and is necessary to obtain the research information desired.

The risks of the Physical well-being.

While there is a risk of injury when doing any activity, injuries from participating in our study are very unlikely. Walking during gait analysis, during gait training, and under free-living conditions are the only activities that could be viewed as having a remote risk of injury. The risk should be no greater than while walking in any environment or while walking on a treadmill in a gym. In the previous six years that our colleagues have been studying gait training using haptic feedback and treadmill walking, more than 65 subjects have been tested and there have been no injuries or complaints from subjects.

The risks of the Psychological well-being.

None

The risks of the Economic well-being.

None

The risks of the Social well-being.

None

Overall evaluation of Risk.

Low - innocuous procedures such as phlebotomy, urine or stool collection, no therapeutic agent, or safe therapeutic agent such as the use of an FDA approved drug or device.

b) If you are conducting international research, describe the qualifications/preparations that enable youto both estimate and minimize risks to participants. Provide an explanation as to why the research must be completed at this location and complete the [LINKFORINTERNATIONALREASEARCHFORM] International Research Form. If not applicable,enter N/A.

N/A

c) Describe the planned procedures for protecting against and minimizing all potential risks. Include the

means for monitoring to detect hazards to the participant (and/or to a potential fetus if applicable).Include steps to minimize risks to the confidentiality of identifiable information.

All subjects are free to withdraw at any time.
There is a potential risk of the strong magnetic field of the MRI scanner attracting ferromagnetic (material with a high magnetic permeability) or metallic objects toward the magnet. For this reason, subjects will be screened for metallic objects in their possession before entering the magnet room. All such metallic objects will be collected and placed in a locker outside of the magnet room. Subjects will also be screened for potentially dangerous metal in their body (e.g., shrapnel). Subjects who may have potentially dangerous metal in their body will be excluded from the study. During the scanning session, the magnet will make intermittent, loud, knocking noises that could cause ear discomfort in some people. Even though this noise is within safety levels, subjects will still be asked to wear ear-plugs (which will not interfere with their ability to communicate with the magnet operator) to minimize this discomfort. Women of child-bearing potential will take a urine pregnancy test prior to MRI. Pregnant women will be not be studied. Some people feel claustrophobic in the magnet; the study will be ended early if this is or becomes a problem for the study subject.

For individuals unaccustomed to walking on a treadmill, we will have them practice treadmill walking while holding onto the handrail until they feel comfortable walking on the treadmill.
During administration and completion of research related questionnaires, no identifiable information will be recorded, thus minimizing any privacy risk. There is no known risks associated with the completion of the forms.

Research data for each subject will be identified by a code sequence and not by any patient identifiers. Linkage codes will be maintained in a locked filing cabinet in the locked office of the PI.

d) Explain the point at which the experiment will terminate. If appropriate, include the standards for the termination of the participation of the individual participant Also discuss plans for ensuring necessary medical or professional intervention in the event of adverse effects to the participants.

Experiments involving a specific subject will terminate anytime the subject wants to stop.

The study will terminate once data is collected from and processed for 104 subjects who have completed the entire 52-week intervention (estimated to take 4 to 5 years). It is possible that further analysis of the data will continue past that point, however, all of the data will be de-identified.

e) Data Safety and Monitoring Plan (DSMP). See guidance on Data Safety and Monitoring.

A Data and Safety Monitoring Plan (DSMP) is required for studies that present Medium or High risk to participants. (See Overall Evaluation of Risk above). If Low Risk, a DSMP may not be necessary. Multi-site Phase III clinical trials funded by NIH require the DSM Plan to have a Data Safety Monitoring Board or Committee (DSMC or DSMB). The FDA recommends that all multi-site clinicaltrials that involve interventions that have potential for greater than minimal risk to study participantsalso have a DSMB or DSMC.

The role of the DSMC or DSMB is to ensure the safety of participants by analyzing pooled data fromall sites, and to oversee the validity and integrity of the data. Depending on the degree of risk and thecomplexity of the protocol, monitoring may be performed by an independent committee, a board (DSMC/DSMB), a sponsor's Data Safety Committee (DSC), a Medical Monitor, a sponsor's safetyofficer, or by the Protocol Director (PD).

Describe the following:

What type of data and/or events will be reviewed under the monitoring plan, e.g. adverse events, protocol deviations, aggregate data?

Adverse events and protocol deviations.

Identify who will be responsible for Data and Safety Monitoring for this study, e.g. Stanford Cancer Institute DSMC, an independent monitoring committee, the sponsor, Stanford investigatorsindependent of the study, the PD, or other person(s).

The Protocol Director for our study, Dr. Julie Kolesar, will monitor participant and data safety.

Provide the scope and composition of the monitoring board, committee, or safety monitor, e.g., information about each member's relevant experience or area of expertise. If the Monitor is the

Our study has minimal risk, therefore we feel that data and safety monitoring can be accomplished by a single individual without the need for a DSMC/DSMB. The protocol director, Dr. Julie Kolesar, along with the study personnel have extensive human subjects research experience and are well qualified to monitor participant and data safety without formal oversight from a DSMC/DSMB.

Stanford Cancer Center DSMC or the PD, enter N/A.

Confirm that you will report Serious Adverse Events (SAEs), Suspected Unexpected Serious Adverse Reactions (SUSARs), or Unanticipated Problems (UPs) to the person or committee monitoring the study in accordance with Sponsor requirements and FDA regulations.

Confirmed.

If applicable, how frequently will the Monitoring Committee meet? Will the Monitoring Committee

Dr. Kolesar will meet quarterly with study personnel.

provide written recommendations about continuing the study to the Sponsor and IRB?

Specify triggers or stopping rules that will dictate when the study will end, or when some action is required. If you specified this in Section 2g [Study Endpoints], earlier in this application enter 'See2g'.

See 2g

Indicate to whom the data and safety monitoring person, board, or committee will disseminate the outcome of the review(s), e.g., to the IRB, the study sponsor, the investigator, or other officials, as

Dr. Kolesar will disseminate the outcome of her reviews to the IRB as appropriate.

appropriate.

Select One:

Y The Protocol Director will be the only monitoring entity for this study.

This protocol will utilize a board, committee, or safety monitor as identified in question #2 above.

6. Benefits

7. Describe the potential benefit(s) to be gained by the participants or by the acquisition of importantknowledge which may benefit future participants, etc.

The information obtained during these studies will help advance medical research that could lead to improved conservative treatments for knee osteoarthritis (OA). Potential advantages include earlier treatment that changes the time course of OA progression. Based on our past studies of this type of gait training, and studies in theliterature suggesting the benefits of

increased walking, all subjects are expected to experience some reduction in knee pain.

8. Privacy and Confidentiality

Privacy Protections

a) Describe how the conditions under which interactions will occur are adequate to protect the privacy interests of participants (e.g., privacy of physical setting for interviews or data collection, protectionsfor follow-up interactions such as telephone, email and mail communications).

Initial identification of potential participants will be done by a patient's personal physician who will be familiar with our study or by a subject seeing a flyer or advertisement containing contact information for a study team member. Subsequent interactions with potential participants by an approved member of the study team will occur by telephone for answering additional questions a potential participant might have, or in person in a private, laboratory setting, for any subject who prefers to meet in person.

Confidentiality Protections

b) Specify PHI (Protected Health Information). PHI is health information linked to HIPAA identifiers (see above). List BOTH health information AND HIPAA identifiers. If you are using STARR, use theData Privacy Attestation to ensure that your request will match your IRB-approved protocol. Be consistent with information entered in section 15a.

The following protected health information and individually identifiable information will be obtained from each subject: name; gender; race/ethnicity; social security number; date of birth; telephone number; address; height; weight; knee X-rays; knee MRIs; lower extremity health history; gait findings; pain scale findings; knee health questionnaire findings.

For participants who are veterans and who are already entered into the VA Computerized Patient Record System (CPRS), we may access the participant's medical record to verify any medical conditions that may be relevant to the research study. For participants who are not veterans or not already entered into CPRS, the VA requires that we enter specific individually identifiable information about them. The information we are required to enter includes: name, gender, address, phone number, date of birth, and social security number. For all participants, certain dates may also be entered into CPRS, such as date of consenting, and date of X-rays or MRI. We may also acquire photographs or video of

participants while performing any research-related tasks. This information will be stored on a secure VA server.
A search of Electronic Medical Records at Stanford and the VA (CPRS) will be conducted to identify potential participants.
We will be looking at the following categories of Health Information, where * denotes embedded identifiers:
B. Coded Diagnoses and Procedures
E.* Images and Imaging Reports with embedded identifiers
F.* Demographics with embedded identifiers

We will be obtaining, using and potentially disclosing to others the following PHI:
E. Images and Imaging Reports with embedded identifiers
F. Demographics with embedded identifiers
1. Names
3. Telephone numbers
4. Address (All geographic subdivisions smaller than a State)
5. Dates more precise than year only, e.g. date of birth or death, date of service, diagnosis, admission
7. Electronic mail addresses
8. Medical record numbers
13. Device identifiers and serial numbers
18. Any other unique identifying number, characteristic, or code excepting only study-specific coded 'identifiers' (study IDs).

PLEASE NOTE that when working with clinical documents and reports, the Privacy Office stipulates that the IRB must list all of PHI elements 1, 3, 4, 5, 7, 8 and 18. The inclusion of these elements in this section may merely be intended to document the risk of inadvertent exposure to these elements and may not represent intended research use of these elements.

The data will be secured by storing it on AMIE compliant desktop or laptop, or on a secure VA server behind the VA firewall.

c) You are required to comply with University Policy that states that ALL electronic devices: computers (laptops and desktops; OFFICE or HOME); smart phones; tablets; external hard disks, USB drives, etc. that may hold identifiable participant data will be password protected, backed up, and encrypted.See http://med.stanford.edu/datasecurity/ for more information on the Data Security Policy and links to encrypt your devices.

Provide any additional information on ALL data security measures you are taking. You must use secure databases such as https://researchcompliance.stanford.edu/panels/hs/redcap RedCap. If you are unsure of the security of the system, check with your Department IT representative. Please see http://med.stanford.edu/irt/security/ for more information on IRT Information Security Services and http://www.stanford.edu/group/security/securecomputing/mobile_devices.html for more information for securing mobile computing devices. Additionally, any PHI data on paper must be secured in an

locked environment.

By checking this box, You affirm the aforementioned. Y

Any paper items containing PHI or III (e.g., linkage codes) will be kept in a locked filing cabinet in Dr. Kolesar's locked office at the VA, or in a locked filing cabinet in a locked room at the VA designated for the storage of human subjects documents (e.g., signed informed consent and HIPAA documents). Any electronic files containing PHI or III will be stored in an electronic folder assigned to Dr. Kolesar that is located on a secure VA server behind the VA firewall.

De-identified data in electronic format will be stored on a secure VA server behind the VA firewall or on password protected, encrypted Stanford computers. Collection of de-identified, coded data will occur on password-protected computers. Data analysis will only occur on de-identified data and will occur on password-protected computers.

d) Describe how data or specimens will be labeled (e.g. name, medical record number, study number,linked coding system) or de-identified. If you are de-identifying data or specimens, who will be responsible for the de-identification? If x-rays or other digital images are used, explain how and bywhom the images will be de-identified.

All data for each subject will be identified by a unique code (see f below). All other identifiers will be removed. Dr. Kolesar or an approved study coordinator willprovide the code to any study team member working with data needing to be de-identified.
All knee MRIs and X-rays will be de-identified, coded, exported from the acquisitionsystems, and stored on a VA server behind the VA firewall. De-identified and coded MRIs and X-raysmay also be stored on a secure Stanford server.
De-identified photos and videos may also be stored on a VA server behind the VA firewall or on a secure Stanford server. These photos and videos will not include the face of the participant, or have it removed before storage for de-identification.

e) Indicate who will have access to the data or specimens (e.g., research team, sponsors, consultants) and describe levels of access control (e.g., restricted access for certain persons or groups, access to linked data or specimens).

All members of the study team will have access to the de-identified (coded) data.

f) If data or specimens will be coded, describe the method in which they will be coded so that study participants' identities cannot be readily ascertained from the code.

When a participant enrolls in the study, they will be assigned a

unique code number selected
from a list of 200, non-repeated, 3-digit, random numbers
(www.random.org/strings). All
data for a given participant will be stored using their unique code
number. Participants'
identities will not be discernable from their code number.

g) If data or specimens will be coded, indicate who will maintain the key to the code and describe how itwill be protected against unauthorized access.

Dr. Kolesar will maintain the key to the code. The key will be stored
in an electronic file
stored on a secure VA server behind the VA firewall. The file with
the key code will be
password protected and only Dr. Kolesar and the study coordinator
will have access to the
file.

h) If you will be sharing data with others, describe how data will be transferred (e.g., courier, mail) or transmitted (e.g., file transfer software, file sharing, email). If transmitted via electronic networks, describe how you will secure the data while in transit.See http://www.stanford.edu/group/security/securecomputing/ http://www.stanford.edu/group/security/securecomputing/. Additionally, if you will be using or sharing

Data will not be shared outside of the study team. Hardcopy materials
transmitted from Stanford to the VA will be hand-carried by members
of
the study team and those forms will be de-identified if possible
(e.g.,
de-identified Lucas Center MRI scanning safety forms, or VA
reimbursement forms).

PHI see https://uit.stanford.edu/security/hipaa https://uit.stanford.edu/security/hipaa.

i) How will you educate research staff to ensure they take appropriate measures to protect the privacy of participants and the confidentiality of data or specimens collected e.g. conscious of oral and written communications, conducting insurance billing, and maintaining paper and electronic data?

All members of the research team will complete all required trainings
mandated by the
research office - including all human subjects related research. Only
the assigned subject
code numbers will be used in all communications about individual
data. In her regular
meeting with the research team, Dr. Kolesar will discuss and
reinforce the importance of
privacy and data security.

9. Potential Conflict of Interest

Investigators are required to disclose any financial interests that reasonably appear to be related/li to thisprotocol.

Financial Interest Tasks

Investigators	Role	Potential COI?	Date Financial Interest Answered	Date OPACS Disclosure Submitted	COI Review Determination
Scott L Delp	OP	N	05/12/2021		
Garry Evan Gold	OP	N	05/11/2021		
Julie Ann Kolesar	PD	N	05/11/2021		

10. Consent Background

13. 1 Waiver of Documentation Phone ScriptCheck if VA related

a) Describe the informed consent process. Include the following.

i) Who is obtaining consent? (The person obtaining consent must be knowledgeable about the study.)

ii) When and where will consent be obtained?

iii) How much time will be devoted to consent discussion?

iv) Will these periods provide sufficient opportunity for the participant to consider whether or not to participate and sign the written consent?

v) What steps are you taking to minimize the possibility of coercion and undue influence?

vi) If consent relates to children and if you have a reason for only one parent signing, provide thatrationale for IRB consideration.

(i) Julie Kolesar, the Protocol Director or her research staff in the Human Performance Lab will be conducting the phone screen. (ii) Verbal consent for collecting information over the phone will be obtained before initiating the phone screen. (iii) 5 minutes at the beginning of the phone call. (iv) Yes. (v) The phone screener will assure the potential subject that their willingness to participate in the phone screen will have no bearing on their routine medical treatment. (vi) N/A

b) What is the Procedure to assess understanding of the information contained in the consent? How will the information be provided to participants if they do not understand English or if they have a hearing impairment? See HRPP Chapter12.2 for guidance.

The phone screen will only include subjects who can understand English and do not have a hearing impairment.

c) What steps are you taking to determine that potential participants are competent to participate in the decision-making process? If your study may enroll adults who are unable to consent, describe (i) howyou will assess the capacity to consent, (ii) what provisions will be taken if the participant regains the capacity to consent,(iii) who will be used as a legally authorized representative, and (iv) what provisions

Before continuing to the screening questions, we will ensure that the participant understands the risks of the phone screen and understands the screening activity. This will be judged by a conversation before asking the subject if they agree to participate in the screening procedure.

will be made for the assent of the participant.

Select ALL of the following regulatory criteria for a waiver of documentation (signature) and provide aprotocol-specific justification:

1) 45 CFR 46·117(c)(i)., that the only record linking the participants and the research would be the consent document, and the principal risk would be potential harm resulting from a breach of confidentiality; each participant (or legally authorized representative) will be asked whether he/she wants documentation linking the participant with the research, and the participant's

wishes govern.

2) **45 CFR 46·117(c)(ii)., that the research presents no more than minimal risk of harm to participants and involves no procedures for which written consent is normally required outsideof the research context.**

3) **45 CFR 46·117(c)(iii)., if participants or legally authorized representatives (LAR) are membersof a distinct cultural group in which signing forms is not the norm, the research presents no more than minimal risk and there is an appropriate alternative mechanism for documenting that informed consent was obtained.**

4) Y **21 CFR 56·109(c)(1)., presents no more than minimal risk of harm to participants and involvesno procedures for which written consent is normally required outside of the research context.**

Rationale for above selection:

This phone screen poses minimal risk to the participant. The only potential harm is a breech in confidentiality. This information is stored securely.

13. 2 Consent 2019 VA Consent Gait Training_embeddedHIPAA

Check if VA related Y

a) **Describe the informed consent process. Include the following.**

i) **Who is obtaining consent? (The person obtaining consent must be knowledgeable about the study.)**

ii) **When and where will consent be obtained?**

iii) **How much time will be devoted to consent discussion?**

iv) **Will these periods provide sufficient opportunity for the participant to consider whether or not to participate and sign the written consent?**

v) **What steps are you taking to minimize the possibility of coercion and undue influence?**

vi) **If consent relates to children and if you have a reason for only one parent signing, provide thatrationale for IRB consideration.**

Dr. Kolesar or a member of her study team will obtain consent from participants. The subject will be assured that he/she has as much time as necessary to review the consent document and ask any questions. Any study team member who obtains consent will be fully trained in the consenting process and fully knowledgable about the study.

b) **What is the Procedure to assess understanding of the information contained in the consent? How will the information be provided to participants if they do not understand English or if they have a hearing impairment? See HRPP Chapter12.2 for guidance.**

The person obtaining consent will ask the participant if he/she has questions about the information contained in the consent or about the study. We do not expect to enroll anyone with whom there will be difficulty communicating nor will we enroll any non-English speakers and this will be determined from the initial contact.

c) **What steps are you taking to determine that potential participants are competent to participate in the decision-making process? If your study may enroll adults who are unable to consent, describe (i) howyou will assess the capacity to consent, (ii) what provisions will be taken if the participant regains the capacity to consent,(iii) who will be used as a legally authorized representative, and (iv) what provisions will be**

We will not recruit subjects who are unable to consent. Subjects will arrange for their own transportation to the study location. There is therefore sufficient reason to believe that they will be participating at their own free will. The research team will repeatedly remind the subject that they may withdraw at any time. To assess their capacity to consent, the research team will pause throughout the consent process to ask for understanding. Before obtaining consent, the team will ask the subject to state the activities and associated risks that would be consenting to in order to ensure that they are competent to consent.

made for the assent of the participant.

Additional VA questions:

i) **List the people to whom you have formally delegated responsibility to obtain informed consent, andstate whether they have the appropriate training to perform this activity.**

Dr. Kolesar, Mr. Uhlrich, Ms. Berkson, or Ms. Vijayakumar will obtain all consents. These people have or will have completed appropriate training and each will have prior experience or specific training in performing consents.

i) Will legally effective informed consent be obtained from the participant or the participant's legally authorized representative (LAR) or both? If LAR, is it clear who can serve as LAR?

Legally effective informed consent will be obtained from each participant. No LARs will be used.

ii) Will the circumstances of the consent process minimize the possibility of coercion or undue influenceand provide the prospective participant or their representative sufficient opportunity to consider whether to participate?

Yes

iii) Will the circumstances of the consent process minimize the possibility of coercion or undue influence?

Yes

iv) Will the information being communicated to the participant or the representative during the consent process exclude any exculpatory language through which the participant or the representative is madeto waive or appear to waive the participant's legal rights, or release or appear to release the investigator, the sponsor, the institution, or its agent from liability for negligence (e.g. I give up any property rights I may have in bodily fluids or tissue samples obtained in the course of the research)?

Yes

v) Please confirm the following:

- **a. A witness to the participant's signature or the participant's legally authorized representative'ssignature will sign and date the consent document.**
- **b. If the sponsor or the IRB requires a witness to the consenting process in addition to the witness tothe participant's signature and if the same person is needed to serve both capacities, a note to thateffect is placed under the witness's signature line.**
- **c. A copy of the signed and dated consent document will be given to the person signing the consentdocument.**
- **d. The consent form is on the VA Form 10-1086.**

13. 3 Waiver of Documentation Web QuestionnaireCheck if VA related

a) Describe the informed consent process. Include the following.

i) Who is obtaining consent? (The person obtaining consent must be knowledgeable about the study.)

ii) When and where will consent be obtained?

iii) How much time will be devoted to consent discussion?

iv) Will these periods provide sufficient opportunity for the participant to consider whether or not to participate and sign the written consent?

v) What steps are you taking to minimize the possibility of coercion and undue influence?

vi) If consent relates to children and if you have a reason for only one parent signing, provide thatrationale for IRB consideration.

i, ii) Consent will be obtained on the web as the first question on the questionnaire iii) Reading the consent part of the script takes approximately 5 minutes iv)yes v)The subject is made aware that they may stop participating in the questionnaire at any time vi) N/A

b) What is the Procedure to assess understanding of the information contained in the consent? How will the information be provided to participants if they do not understand English or if they have a hearing impairment? See HRPP Chapter12.2 for guidance.

The questionnaire will only include subjects who can understand English and do not have a hearing impairment.

c) What steps are you taking to determine that potential participants are competent to participate in the decision-making process? If your study may enroll adults who are unable to consent, describe (i) howyou will assess the capacity to consent, (ii) what provisions will be taken if the participant regains the capacity to consent,(iii) who will be used as a legally authorized representative, and (iv) what provisions will be made for the assent of the participant.

The online screening questionnaire poses minimal risk. Following completion of the questionnaire, potential subjects meet in person with qualified study personnel for consenting. During this in-person consent visit, we will assess competency through questions and additional screening.

Select ALL of the following regulatory criteria for a waiver of documentation (signature) and provide aprotocol-specific justification:

1) **45 CFR 46·117(c)(i)., that the only record linking the participants and the research would be the consent document, and the principal risk would be potential harm resulting from a breach of confidentiality; each participant (or legally authorized representative) will be asked whether he/she wants documentation linking the participant with the research, and the participant's wishes govern.**

2) **45 CFR 46·117(c)(ii)., that the research presents no more than minimal risk of harm to participants and involves no procedures for which written consent is normally required outsideof the research context.**

3) **45 CFR 46·117(c)(iii)., if participants or legally authorized representatives (LAR) are membersof a distinct cultural group in which signing forms is not the norm, the research presents no more than minimal risk and there is an appropriate alternative mechanism for documenting that informed consent was obtained.**

4) Y **21 CFR 56·109(c)(1)., presents no more than minimal risk of harm to participants and involvesno procedures for which written consent is normally required outside of the research context.**

Rationale for above selection:

This questionnaire poses minimal risk to the participant. The only potential harm is a breech in confidentiality. This information is stored securely. Stanford's Redcap software is PHI safe.

14. Assent Background (less than 18 years of age)

15. HIPAA Background

15. 1 Waiver of Authorization for recruitment

a) **Describe the protected health information (PHI) needed to conduct screening or recruitment. PHI is health information linked to HIPAA identifiers. List BOTH health information AND HIPAA identifiers. If you are using STARR, use the Data Privacy Attestation to ensure that your request willmatch your IRB-approved protocol.**

Potential volunteers for this study might leave a name, telephone number, and email address so we can contact them to arrange a suitable time for testing (these are the HIPAA identifiers). Pre-screening of potential participants will likely be done by phone to confirm that they meet the inclusion and exclusion criteria, and to obtain contact information. The health information that will be collected during this phone conversation can be seen in the attached phone script. It is an abbreviated version of the inclusion/exclusion criteria. Electronic Medical Record Searches at the VA Hospital (CPRS) and Stanford Hospitals will be conducted to identify potential subjects. We will be looking at the following categories of Health Information, where * denotes embedded identifiers: B. Coded Diagnoses and Procedures E.* Images and Imaging Reports with embedded identifiers F.* Demographics with embedded identifiers We will be obtaining, using and potentially disclosing to others the following PHI: E. Images and Imaging Reports with embedded identifiers F. Demographics with embedded identifiers 1. Names 3. Telephone numbers 4. Address (All geographic subdivisions smaller than a State) 5. Dates more precise than year only, e.g. date of birth or death, date of service, diagnosis, admission 7. Electronic mail addresses 8. Medical record numbers 13. Device identifiers and serial numbers 18. Any other unique identifying number, characteristic, or code excepting only study-specific coded 'identifiers' (study IDs). PLEASE NOTE that when working with clinical documents and reports, the Privacy Office stipulates that the IRB must list all of PHI elements 1, 3, 4, 5, 7, 8 and 18. The inclusion of these elements in this section may merely be intended to document the risk of inadvertent exposure to these elements and may not represent intended research use of these elements. The data will be secured by storing it on AMIE compliant desktop or laptop

a) Please Answer:

Y **Do you certify that the use or disclosure of protected health information involves no more than aminimal risk to the privacy of individuals?**

Y **Do you certify that the research could not practically be conducted with out the waiver?**

Y **Do you certify that you have adequate written assurances that the protected health information willnot be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research project, or for other research for which the use or disclosure of protected health information would be permitted?**

Y **Do you certify that the research could not practically be conducted with out access to and use of the protected health information?**

b) Please describe an adequate plan to protect any identifiers from improper use and disclosure.

The data will be secured by storing it on an AMIE compliant desktop or laptop, or oan a secure VA server behind the VA firewall.

c) Please describe an adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law.

All VA research records will be maintained consistent with existing VA record retention policies.

16. Attachments

Attachment Name	Attached Date	Attached By	Submitted Date
KOOS Questionnaire	05/18/2016	beaupre1	
Walking Activity Log	05/18/2016	beaupre1	
VA Required Questions, Gait Training	05/19/2016	beaupre1	
Full-Sized Flyer	06/13/2016	beaupre1	
Full-Sized Flyer withTear-Offs	06/13/2016	beaupre1	
Quarter-Sized Flyer	06/13/2016	beaupre1	
VA Gait Training Grant	07/14/2016	suhlrich	
Information Sheet - attachedto redcap screen	05/11/2017	suhlrich	
Descriptive Flyer 2	05/11/2017	suhlrich	
Mailling Letter 2	05/11/2017	suhlrich	
Online Advertisement Text 2	05/11/2017	suhlrich	
Recruitment Video	10/02/2017	suhlrich	
Descriptive Flyer 3	10/13/2017	julie14	
Mailing Letter 3	10/13/2017	julie14	
DSMB letter and proposal to disband	10/13/2017	julie14	

Title : Long-Term Effectiveness of Walking Training in Patients with Knee Osteoarthritis
Closed: 01/05/2022

Obligations

The Protocol Director agrees to:

- Adhere to principles of sound scientific research designed to yield valid results
- Conduct the study according to the protocol approved by the IRB
- Be appropriately qualified to conduct the research and be trained in Human Research protection, ethicalprinciples, regulations, policies and procedures
- Ensure all Stanford research personnel are adequately trained and supervised
- Ensure that the rights and welfare of participants are protected including privacy and confidentiality of data
- Ensure that, when de-identified materials are obtained for research purposes, no attempt will be made tore-identify them.
- Disclose to the appropriate entities any potential conflict of interest
- Report promptly any new information, modification, or unanticipated problems that raise risks to participants or others
- Apply relevant professional standards.

Any change in the research protocol must be submitted to the IRB for review prior to the implementation of such change. Any complications in participants or evidence of increase in the original estimate of risk should be reported at once to the IRB before continuing with the project. Inasmuch as the Institutional Review Board (IRB) includes faculty, staff, legal counsel, public members, and students, protocols should be writtenin language that can be understood by all Panel members. The investigators must inform the participants of any significant new knowledge obtained during the course of the research.

IRB approval of any project is for a maximum period of one year. For continuing projects and activities, it is the responsibility of the investigator(s) to resubmit the project to the IRB for review and re-approval prior to the end of the approval period. A Notice to Renew Protocol is sent to the Protocol Director 7 weeks prior to the expiration date of the protocol.

https://stanfordmedicine.box.com/shared/static/qbsi8u8h47qsotxhdpuzz50xlrqa0sgo.pdf Report promptly any new information, complaints, possibly serious and/or continuing noncompliance, or unanticipated problems involving risks to participants or others.

All data including signed consent form documents must be retained for a minimum of three years past the completion of the research. Additional requirements may be imposed by your funding agency, your department, or other entities. (Policy on Retention of and Access to Research Data, Research Policy Handbook,
http://doresearch.stanford.edu/policies/research-policy-handbook/conduct-research/retention-and-access-research-data)APPROVAL LETTER/NOTICE NOTE: List all items (verbatim) that you want to be included in your
approval letter (e.g., Amendment date, Investigator's Brochure version, consent form(s) version(s), advertisement name, etc.) in the box below.

Y By checking this box, I verify that I, as the Protocol Director (PD) responsible for this research protocol, have read and agree to abide by the above obligations, or that I have been delegated authority by the PD tocertify that the PD has read and agrees to abide by the above obligations.

Study Identification

Unique Protocol ID: O1811-R

Brief Title: Long-Term Effectiveness of Walking Training in Patients With Knee Osteoarthritis

Official Title: Personalized Gait Training With Feedback to Reduce Knee Pain From Osteoarthritis

Secondary IDs:

Study Status

Record Verification: August 2021

Overall Status: Terminated [Study data collection was terminated due to COVID-19 pandemic and will not resume.]

Study Start: November 1, 2016

Primary Completion: October 31, 2020 [Actual] Study Completion:

October 31, 2020 [Actual]

First Submitted: May 4, 2016

First Submitted that Met QC Criteria: May 6, 2016

First Posted: May 10, 2016 [Estimate]

Last Update Submitted that Met QC Criteria: August 13, 2021

Last Update Posted: August 20, 2021 [Actual]

Sponsor/Collaborators

Sponsor: VA Office of Research and Development

Responsible Party: Sponsor

Collaborators:

Oversight

U.S. FDA-regulated Drug: No

U.S. FDA-regulated Device: No

Data Monitoring: No

Study Description

Brief Summary: Nearly one out of every two Americans will develop knee osteoarthritis by age 85. Over 20 million Americans, including nearly three million Veterans, currently have painful knee arthritis that limits their daily activity or recreation. The vast majority of those individuals will be prescribed anti-inflammatory drugs that provide some pain relief but do not slow the progression of the disease. Often people with knee arthritis are told they must live with the pain until they become appropriate candidates for knee replacement surgery, but that can require tolerating the pain and limiting function for many years. Because of other health issues, some individuals are never acceptable surgery candidates. What is desperately needed are better conservative approaches for treating these patients. Two such approaches will be tested and compared in this study.

Detailed Description: This study is a randomized controlled trial to investigate conservative treatments for individuals with painful knee osteoarthritis (OA). The study will recruit participants who have isolated, medial compartment knee OA. Subjects will be assigned to one of two gait training groups. Both groups will undergo gait analysis to determine their foot progression angle at their comfortable walking speed. Both groups will receive personalized gait retraining to either alter their foot progression angle or to achieve consistency of their natural foot progression angle.

Gait retraining will consist of once a week sessions for six weeks. The gait training will use a fading feedback approach, where the percentage of each weekly session during which feedback is used is decreased from week to week until no feedback is used by the last training session. Throughout the six-week training period subjects will be encouraged to practice their gait for at least ten minutes per day. Subjects will continue to practice their gait throughout the remainder of the 52-week intervention. Subjects will have their walking activity recorded using a 3-axis pedometer. Compared to their baseline walking activity, participants will be instructed to increase their daily walking by ten minutes per day throughout the 52-week intervention.

All subjects will receive monthly phone calls to encourage maintaining a regular walking regimen. Walking activity will be monitored periodically using a pedometer. Subjects will receive knee MRIs

and weight-bearing knee radiographs at the start and end of the study. All participants will complete pain evaluations and clinical knee score questionnaires during the study. The investigators expect that subjects in both groups will have a reduction in knee pain over the course of the 52-week intervention. The primary objective of the study it to determine if the change in pain between baseline and week 52 is different between the two groups.

Conditions

Conditions: Osteoarthritis

Keywords: Osteoarthritis, Knee
Arthritis
Joint Diseases Musculoskeletal Diseases
Rheumatic Diseases

Study Design

Study Type: Interventional

Primary Purpose: Treatment

Study Phase: Not Applicable

Interventional Study Model: Parallel Assignment

Number of Arms: 2

Masking: Single (Participant) Allocation: Randomized Enrollment: 68
[Actual]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Gait Training; Altered Foot Progression Angle Participants will receive personalized gait training while walking on a treadmill with real-time, haptic feedback. The goal of the training is to encourage participants to adopt an altered foot progression angle in an attempt to alter the distribution of forces crossing the knee joint. Training will occur once a week for six weeks. This will be followed by a 46-week home and community-based walking program to practice and internalize the new personalized, gait pattern and to encourage daily walking. Refresher training with haptic feedback will be offered at weeks 11, 25 and 39 to enhance internalization of the new foot progression angle.	Gait Training; Altered Foot Progression Angle Participants will receive personalized gait training while walking on a treadmill with real- time, haptic feedback to encourage them to adopt a new foot progression angle. Participants will walk for an additional ten minutes per day to internalize their new foot progression angle over 52 weeks.
Experimental: Gait Training; Consistent Foot Progression Angle Participants will receive personalized gait training while walking on a treadmill with haptic feedback. The goal of the training is to encourage participants to maintain a consistent foot progression angle in an attempt to minimize the variability in the forces crossing the knee joint. Training will occur once a week, for 6 weeks. This will be followed by a 46-week home and community-based walking program to encourage daily walking. Refresher training with haptic feedback will be offered at weeks 11, 25 and 39 to maintain foot progression angle consistency.	Gait Training; Consistent Foot Progression Angle Participants will receive personalized gait training while walking on a treadmill with haptic feedback to encourage them to maintain a consistent foot progression angle. Participants will walk an additional ten minutes per day to internalize the consistency of their foot progression angle over 52 weeks.

Outcome Measures

Primary Outcome Measures:

1. Change in Knee adduction moment
[Time Frame: Change between baseline and week 52]

Change in magnitude of the more prominent peak in the knee adduction moment profile between baseline and week 52

2. Change in Knee Pain
[Time Frame: Change between baseline and week 52]

11-point Numeric Rating Scale for medial knee pain assessed

Secondary Outcome Measures:

1. Cartilage MRI properties
[Time Frame: Change between baseline and week 52]

Change in cartilage properties assessed via MRI between baseline and week 52

☐ Eligibility

Minimum Age: 18 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Diagnosed with isolated, medial compartment knee OA of at least six months duration

- Kellgren-Lawrence grade of I, II, or III
- Age greater than 18 years at the time of enrollment
- Ability to give informed consent
- Knee pain more than three days per week on average
- Average knee pain in medial compartment between 3 and 9 on an 11-point Numerical Rating Scale, and greater than pain in other compartments
- Ambulatory without aids
- Able to walk for at least 25 consecutive minutes
- Able to walk on treadmill safely at 0·7 m/s or faster
- Able to reduce the prominent peak of the knee adduction moment by changing foot progression angle

Exclusion Criteria:

- Body mass index equal to or greater than 35
- Pregnancy
- Plans for knee replacement within the next 12 months
- Contraindications to MRI
- Nerve or muscle disease associated with walking difficulty
- Narcotic pain medication usage
- History of rheumatoid arthritis or autoimmune disease
- An episode of gout or pseudogout in the knee in the past year
- History of neuropathic arthropathy, infectious disease, or other major systemic diseases
- Current or recent past use (within two months) of oral corticosteroids
- Cognitive impairments that would limit a subject's understanding
- Expecting a significant change in activity level or weight within the next 12 months
- Regularly participates in high impact activities such as running, soccer, basketball, etc.
- Unable to perform the 3rd stage of the 4-stage balance test, which involves holding a tandem stance for 10 seconds

The following criteria apply only to the affected osteoarthritic limb:

- History of symptomatic arthritis in lower limb joints other than the knees that is more severe than knee arthritis
- Replacement of any lower extremity joint
- Lateral tibiofemoral joint space width less than medial
- Recurrent giving way of the knee
- Symptoms arising primarily from a meniscal or ligament pathology or other structure not directly related to osteoarthritis as identified by physical exam, health record, or MRI
- Symptoms originating primarily from the patellofemoral joint

- Avascular necrosis
- Recent (within two months) knee injury or surgery
- Planned use of hinged knee brace in next 12 months
- Severe knee malalignment of more than 10 degrees from neutral
- Intra-articular injection within the past 2 months or planned for the next 12 months

Contacts/Locations

Study Officials: Julie Kolesar,

PhD Principal Investigator

VA Palo Alto Health Care System, Palo Alto, CA

Locations: United States, California

VA Palo Alto Health Care System, Palo Alto, CA

Palo Alto, California, United States, 94304-1290

Stanford University, Depts: Bioengineering; Orthopaedics

Stanford, California, United States, 94305

IPDSharing

Plan to Share IPD: No

References

Citations:

Links:

Available IPD/Information:

Summary of Changes to Protocol

The following list summarizes all changes made to the IRB protocol and clinicaltrials.gov during the course of the study.

Date	Document	Description of Changes
June 16, 2016	IRB clinicaltrials.gov	Initial protocol submitted
July 19, 2016	IRB	Initial protocol accepted
August 24, 2016	clinicaltrials.gov	New language has been added to the ICD (just prior to the Participant Responsibilities section) to make clear that data are to be stored for future research use. This was previously stated in the HIPAA document, but now it is also stated in the ICD. The HIPAA was also changed to state that the authorization to use data in future research has no expiration date. This is a revision from the previous 12/31/2050 date.
November, 08 2016	IRB	Updated Personnel Info of Co-protocol director with new married name: Julie Kolesar (previous name was Julie Thompson).
November, 09 2016	IRB	• We will be performing electronic medical record searches of EPIC at Stanford (through STRIDE), and of CPRS at the VA hospital. We will send an advertisement letter (paper mail) to potential participants that we identify. • In our consent form, we added the option to give subjects a recruitment card for another IRB-approved arthritis study (IRB# 3780) currently occurring at Stanford/VA that may be of interest to them. • We removed some intermediate visits from the visit schedule in the consent form.
November 10, 2016	clinicaltrials.gov	• Study status changed to 'Recruiting' • Oversight changed to include Data Monitoring • Inclusion criteria edited to include participants over 18 years of age and no maximum age, knee pain 3 days/week on average, and ability to walk safely on a treadmill • Exclusion criteria edited to include an expected significant change in activity level or weight within the next 12 months • Julie Kolesar, PhD added as a sub-investigator and central contact backup
December, 21 2016	IRB	• Consolidated several exclusion criteria into one: "Symptoms arising primarily from a meniscal or ligament pathology as identified by physical exam, health record, or MRI." • Added a question to phone script for us to be able to access medical records in order to place x-rays or assess old diagnoses prior to first visit. • Added question to phone screen asking if they would be interested in learning about Dr. Robinson's protocol during their first visit. This allows us to coordinate with Dr. Robinson's team prior to their visit. • Consent form - we ask if we can pass contact information to Dr. Robinson's group to facilitate contact between the participant and Dr. Robinson's group if participants are interested. • We added text and a detailed flyer in order to advertise online and in print. 8g was updated accordingly.
February, 06 2017	IRB	• We specified some of the exclusion criteria for only the involved osteoarthritic limb. • The following criteria apply only to the affected osteoarthritic limb: History of symptomatic arthritis in lower limb joints other than the knees Replacement of any lower extremity joint History of lower limb fracture or surgery requiring hospitalization Lateral tibiofemoral joint space width less than medial Recurrent giving way of the knee Symptoms arising primarily from a meniscal or ligament pathology as identified by physical exam, health record, or MRI Symptoms originating primarily from the patellofemoral joint Avascular necrosis History of knee buckling or recent (within two months) knee injury Planned use of hinged knee brace in next 12 months Severe knee malalignment of more than 5 degrees from neutral Intra-articular injection within the past 2 months or planned for the next 12 months
May 9, 2017	clinicaltrials.gov	Oversight updated to specify “No use of FDA-regulated drug or device” Study description changed from specifying a visual analog pain evaluation to pain evaluation. The tool for collecting the knee pain outcome measure changed from a visual analog scale to a numeric rating scale. All previous visual analog pain scores were converted to numerical rating scale scores by rounding to the nearest whole number. These scoring systems

		correspond, but the numeric rating scale is seen as superior as it is easier to understand (Hjermstad et al., 2010, *J Pain Symptom Manag, **41**(6))* The following exclusion criteria were changed to apply only to the affected osteoarthritic limb: history of symptomatic arthritis in lower limb joints other than the knee, replacement of any lower extremity joint, history of lower limb fracture or surgery requiring hospitalization, lateral tibiofemoral joint space width less than medial, recurrent giving way of the knee, symptoms arising primarily from a meniscal or ligament pathology as identified by physical exam, health record or MRI, symptoms originating primarily from the patellofemoral joint, avascular necrosis, history of knee buckling or recent (within 2 months) knee injury, planned use of hinged knee brace in next 12 months, severe knee malalignment of more than 5 degrees from neutral, intra-articular injection within the past 2 months or planned for the next 12 months
May 11, 2017	clinicaltrials.gov	Study Phase changed from 'Phase 2' to 'Not Applicable'
May 16, 2017	IRB	Exclusion criteria added and removed. A few criteria needed to also be more specific. The main addition is excluding subjects who regularly participate in high impact activities ('Regularly participates in high impact activities such as running, soccer, basketball, etc.'). We also widened the allowable limb alignment to ±10° (from ±5°). We added a minimum treadmill walking speed (0·7 m/s or faster) and removed the lower limb fracture exclusion as it is lumped into another criteria. • We will be using RedCap for data collection and subject contacting, so "Stanford University collaborating research staff and officials responsible for the administration and conduct of research" was added to the disclosure list on the HIPAA form. • The x-ray views were updated, resulting in a 0·004 milliSv reduction in radiation exposure, or 12 hours of background radiation. Sections 1 and 4 as well as the consent form have been updated. • We added a member to the research team (Melody Cardona, Clinical Research Assistant • We removed the "has not had a hip/knee replacement" from the mailing letter and detailed flyer • If subjects are not comfortable walking on the treadmill at the week 0 visit, they have the option to visit the Stanford Human Performance Lab to practice treadmill walking under the supervision of the study team. • The phone screen and consent forms were updated in accordance with above changes • A descriptive flyer was added to be used as advertisement, potentially in newspapers ("Subjects (veterans and non-veterans) will first learn about the existence (but not specific study details) of the VA study of a new conservative treatment for medial compartment knee OA from a variety of sources, including word-of-mouth, their health care provider(s) at VA, or from other Bay Area clinicians (who are aware of the existence of the study via word-of-mouth), and posted flyers. We will also consider advertising via newspapers and the internet to achieve our recruitment targets." • A web questionnaire (on RedCap) has been added to supplement our phone screen. The phone screen may still be used if potential subjects prefer it • A few words were modified in the online advertisement text file
May 22, 2017	IRB	Uploaded correct HIPAA document in section 15 (old consent doc previously displayed there).
July, 18 2017	IRB	Review, no changes
October, 04 2017		We added the use of video in section 8g ("Informational audio and visual material will be used for recruitment as approved by the IRB")
October 31, 2017	clinicaltrials.gov	• Inclusion criteria updated to specify average knee pain between 3 and 9 on an 11-point Numerical Rating Scale, and the ability to walk on a treadmill safely at 0·7 m/s or faster • Exclusion criteria for gout changed to specify an episode of gout or pseudogout in the knee in the past year • Addition of exclusion criteria for regular participation in high impact activities such as running, soccer, basketball, etc. • Edits to exclusion criteria applying only to the affected osteoarthritic limb (changes italicized): history of symptomatic arthritis in lower limb joints other than the knee that is more severe than knee arthritis, symptoms arising primarily from a meniscal or ligament pathology or other structure not directly related to osteoarthritis, recent (within 2 months) knee injury or surgery, and severe knee malalignment of more than 10 degrees from neutral
November, 17 2017	IRB	• Added Becky Lambach to study personnel • Updated study procedures in section 2 to clarify type of pain scale used (from "Visual Analog Scale" to "standardized pain scale") and amount of walking involved ("Subjects will

		walk 10-minutes per day more than their historical average throughout the 52-week intervention.") • Edited knee pain inclusion criteria in section 8h to specify medial pain • Updated section 9 to state that participant and data safety will be monitored by our PD instead of a formal DSMB. Our study is low risk, and the first DSMB review revealed no adverse events whatsoever. The head of our DSMB himself proposed to disband, and a signed letter from him is included in section 16. • Added race/ethnicity to list of PHI obtained from participants • Updated consent document to more clearly specify medial pain, amount of walking involved, and that subjects will not receive a copy of their research MRI (changes tracked in document) • Updated online screening questionnaire to include race/ethnicity questions. The online questionnaire may now also be accessed via website links. Competency of qualifying individuals will be assessed in person at the consent visit. • Uploaded new descriptive flyer in section 16 • Uploaded new recruitment mail-out in section 16 • Uploaded DSMB letter (and proposal to disband with justification) in section 16
October 31, 2017	clinicaltrial.gov	• Inclusion criteria updated to specify average knee pain between 3 and 9 on an 11-point Numerical Rating Scale, and the ability to walk on a treadmill safely at 0·7 m/s or faster • Exclusion criteria for gout changed to specify an episode of gout or pseudogout in the knee in the past year • Addition of exclusion criteria for regular participation in high impact activities such as running, soccer, basketball, etc. • Edits to exclusion criteria applying only to the affected osteoarthritic limb (changes italicized): history of symptomatic arthritis in lower limb joints other than the knee that is more severe than knee arthritis, symptoms arising primarily from a meniscal or ligament pathology or other structure not directly related to osteoarthritis, recent (within 2 months) knee injury or surgery, and severe knee malalignment of more than 10 degrees from neutral
April, 06 2018	IRB	Nikki Taylor has also been added to the protocol.
May, 03 2018	IRB	Added Brittany Presten to the Personnel list.
May 3, 2018	clinicaltrials.gov	• Data Monitoring oversight changed from 'Yes' to 'No' • Knee pain inclusion criteria changed from three days per week on average to more than three days per week on average • Average knee pain inclusion criteria changed to specify pain in the medial compartment between 3 and 9 on an 11-point Numerical Rating Scale, and greater than pain in other compartments • Addition of exclusion criteria for inability to perform the 3rd stage of the 4-stage balance test, which involves holding a tandem stance for 10 seconds
July, 11 2018	IRB	Personnel changes: Added - Madeleine Berkson, Dominic Willoughby, and Valentina Mazzoli Removed - Amy Silder
January, 03 2019	IRB	Evangeline Vijayakumar has been added to Personnel. The Resources section has also been updated to include her qualifications.
February, 01 2019	IRB	• Removed the following personnel, who are no longer assisting with the study: Serena Bonaretti, Melody Cardona, Dominic Willoughby, Brittany Presten, Becky Lambach, and Nikki Taylor. • Updated the consent form to include embedded HIPAA authorization text, as permitted by the new human subjects policies recently issued by the VA. This modification will negate the need for the current standalone HIPAA authorization form.
February, 20 2019	IRB	Added Melissa Boswell to list of personnel
July, 8 2019	clinicaltrials.gov	Study status changed from 'Recruiting' to 'Active, not recruiting'
July, 10 2019	clinicaltrials.gov	Primary outcome measure of 'Pain' changed to 'Change in Knee Pain'
July, 10 2019	IRB	Clarified that 400 subjects expected to be screened/consented and 100 expected to be enrolled.
September, 29 2019	IRB	PI/PD role is being transferred from Dr. Gary Beaupre to Dr. Julie Kolesar. All applicable protocol sections have been updated to reflect this change, including updating the PD and Admin Contact info to Dr. Kolesar and moving Dr. Beaupre to Other Personnel. Consent forms have also been updated (with changes tracked) and uploaded.
January, 07 2020	IRB	Removed Evangeline Vijayakumar from Personnel and added Kirsten Seagers.
February, 27 2020	IRB	Mengfei Yu was added to the list of personnel.

April, 29 2020	IRB	Lukasz Kidzinski was added to the protocol
July, 07 2020	IRB	Removed Madeleine Berkson from protocol and added Andrew Yock, Leyton Ho, and AJ Song.
October 21, 2020	clinicaltrials.gov	Anticipated study completion date changed from October 31, 2020 to September 30, 2021 following approval of project extension by VAORD
November 12, 2020	clinicaltrials.gov	• Study status changed from 'Active, not recruiting' to 'Terminated (Study data collection was terminated due to COVID-19 pandemic and will not resume.)' • Study completion date changed from September 30, 2021 (Anticipated) to October 31, 2020 (Actual) • Enrollment changed from 104 (Anticipated) to 68 (Actual) • 104 was an erroneous calculation at the beginning of the study. We mistakenly added participants to the calculated sample size (80 total) for our expected attrition. This was not necessary given the intent-to-treat analysis plan. The correct initial enrollment target was 80, but this was not updated on clinicaltrials.gov
January 14, 2021		Added Elka Rubin to study personnel

Initial Statistical Analysis Plan

No separate Statistical Analysis Plan was submitted to clinicaltrials.gov for this study. Recruitment for the study began in August 2016, prior to the requirement for including a Statistical Analysis Plan alongside the clinicaltrials.gov registration, which began on January 18, 2017. The initial statistical plan is summarized from the grant application that supported the work (Merit Review Award I01 RX001811 from the United States Department of Veterans Affairs Rehabilitation Research and Development Service), which was submitted on May 29, 2015.

Study Hypotheses - Primary Outcomes
H1: The intervention group will reduce their medial knee pain on the VAS (visual analog scale) more than the sham group.
H2: The intervention group will reduce their peak knee adduction moment more than the sham group.

Study Hypotheses - Secondary Outcomes
SH1: The intervention group will experience slowed cartilage degeneration compared to the sham group, or smaller increases in quantitative MRI measures $T_{1\rho}$ and T_2.

Exploratory Outcomes
We will compare the change in daily steps and the knee osteoarthritis outcome score (KOOS) from the week 0 to year 1 visit between groups.

Sample Size Considerations
Two groups of 40 patients each: a) intervention and b) sham group. The planned sample size is based on the assumption of:

- Effect size of 0·57 based on the change in pain found by Shull and colleagues (Shull, personnel communication) for the intervention group and the change in pain reported by Brosseau et al. for a self-directed walking control group.[7,38]
- Type 1 error is 0·05 (two-sided) and power = 0·80.
- The primary analysis will be intent-to-treat.
- Expected attrition of 24% was accounted for with planned intent-to-treat analyses and missing data methods.[27,39] Every effort was made to collect missing data from participants.

Planned Interim Analysis
There are no planned interim analyses.

Randomization
Subjects will be randomly assigned to either the intervention group or the sham group by opening a sealed envelope indicating group assignment after obtaining informed consent. To ensure balanced numbers in the two groups, randomization will be accomplished using a permuted block design. Randomization will be done using 10 blocks of 8 subjects each, thus ensuring having 4 subjects in each group after every increment of 8 enrollees. We will test if randomization achieved balance between the intervention and sham groups on key confounding variables such as age, gender, baseline pain, baseline BMI, and arthritis (Kellgren Lawrence) grade. If confounding remains, we will add these covariates to the primary regression models.

Statistical Analysis
All analyses will be on the intent-to-treat sample. To minimize potential attrition bias and address missing data, we will conduct multiple imputation. We will impute 40 datasets using the expectation maximization algorithm to maintain population parameters and distributions of the whole sample and to prevent the loss of statistical power. Multiple imputation will be conducted using SAS PROC MI and the imputed datasets will be analyzed in SAS and combined to yield the final parameter estimates and inferences.

We will use repeated measures ANOVA to test for changes in KOOS score and VAS. We will also use t-tests to compare the start-to-end changes in VAS scores and KOOS scores between the intervention and sham group.

Final Statistical Analysis Plan

Study Hypotheses - Primary Outcomes
H1: The intervention group will reduce their medial knee pain on the numeric rating scale (NRS) more than the sham group.
H2: The intervention group will reduce their peak knee adduction moment more than the sham group.

Study Hypotheses - Secondary Outcomes
SH1: The intervention group will experience slowed cartilage degeneration compared to the sham group, or smaller increases in quantitative MRI measures $T_{1\rho}$ and T_2.

Exploratory Outcomes
We will assess between-group differences in the proportion of patients who experienced a reduction in pain >1 points on the NRS scale or a reduction in knee adduction moment peak >5%. We will also assess between-group differences in one-year changes in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain, WOMAC function, and daily steps. Finally, we will assess between-group differences in intervention compliance and foot progression angle accuracy at the year 1 time point.

Sample Size Considerations
Two groups of 40 patients each: a) intervention and b) sham group. The planned sample size is based on the assumption of:

- Effect size of 0·57 based on the change in pain found by Shull and colleagues (Shull, personnel communication) for the intervention group and the change in pain reported by Brosseau et al. for a self-directed walking control group.[7,38]
- Type 1 error is 0·05 (two-sided) and power = 0·80.
- The primary analysis will be intent-to-treat.
- Expected attrition of 24% was accounted for with planned intent-to-treat analyses and missing data methods.[27,39] Every effort was made to collect missing data from participants.

Interim Analysis
An unplanned interim analysis was performed to ensure the quality of MRI data. An issue with an MRI sequence was discovered (not a sequence used to compute $T_{1\rho}$ and T_2), so an analysis was performed on all MRI data after 26 individuals had completed the study. The statisticians who conducted the final analyses did not conduct the interim analyses, it had no bearing on decisions about the trial, and the planned final analyses were not affected.

Randomization
Subjects will be randomly assigned to either the intervention or the sham group by the study coordinator unhiding a row on a spreadsheet after the participant meets all inclusion criteria. To ensure balanced numbers in the two groups, randomization will be accomplished using a permuted block design. Randomization will be done using 10 blocks of 8 subjects each, thus ensuring having 4 subjects in each group after every increment of 8 enrollees. We will test if randomization achieved balance between the intervention and sham groups on key confounding variables such as age, gender, baseline pain, baseline BMI, and arthritis (K-L) grade. If confounding remains, we will add these covariates to the primary regression models.

Statistical Analysis
All analyses will be on the intent-to-treat sample. To minimize potential attrition bias and address missing data, we will conduct multiple imputation. We will impute 25 datasets using the Markov chain Monte Carlo method for Continuous Variables to maintain population parameters and distributions of the whole sample and to prevent the loss of statistical power. Multiple imputation will be conducted using SAS PROC MI and the imputed datasets will be analyzed in SAS and combined to yield the final parameter estimates and inferences.

The primary outcomes (changes in NRS pain and the knee adduction moment peak) will be presented for the intervention and sham groups as means and standard deviations and compared using linear regression models,

adjusting for baseline scores. All participants who were randomized into either group will be included in the intent-to-treat analyses. No multiplicity correction will be used for primary outcomes as the hypotheses are separate.

The secondary outcomes (changes in $T_{1\rho}$ and T_2 in the medial and lateral compartments) will be presented for the intervention and sham groups as means and standard deviations over subjects and compared using linear regression models. All participants who were randomized into either group will be included in the intent-to-treat analyses. Confidence intervals will be reported, but *P*-values will not be reported because there was no pre-specified multiplicity correction for secondary outcomes.

For the proportion exploratory outcomes, proportions will be calculated for the intervention and sham groups and logistic regression will be used to compare the groups. These proportions will be computed using all randomized participants with an intent-to-treat analysis. Linear regression and per-protocol analysis will be used to evaluate all other exploratory outcomes. No multiplicity corrections will be used for exploratory outcomes.

Sensitivity analyses will be performed excluding participants with missing data from institutional shutdown from COVID-19 and participants with missing data from study attrition.

Summary of Changes to Statistical Analysis Plan

In addition to statistical analysis plans not being required for clinical trials that started in 2016, our IRB did not require documentation of changes in the statistical analysis plan, so not all changes to the statistical analysis plan were shown in the IRB or on clinicaltrials.gov. Prior to analyzing the data and breaking the randomization code, we changed some analysis techniques, based on the best modeling approaches at the time and the unexpected disruption of the COVID-19 pandemic. Changes from the original grant to the analysis used in the paper are summarized below.

1) The numeric rating scale (NRS), instead of the visual analog scale (VAS) was used to assess medial knee pain. The anchor points on the scales (no pain: 0 to worst pain imaginable: 10) remained the same. These scales correspond, but the NRS is recommended as it is more interpretable for participants (Hjermstad et al., 2010, J Pain Symptom Manag, **41**(6)). This change was recommended by an external expert on pain assessment, and the change from the continuous (VAS) to discrete (NRS) version of the scale was not deemed problematic, since they measure the same quantity and have been shown to closely correspond. All previously recorded VAS scores (week 0 scores for five intervention and four sham participants) were converted to NRS scores by rounding to the nearest whole number.
2) Randomization was performed by unhiding a row of a spreadsheet, rather than using envelopes.
3) The primary outcomes were compared using linear regression models, adjusting for baseline scores.
4) The secondary outcomes were compared using linear regression models.
5) Exploratory outcomes (the proportion of patients who experienced a reduction in pain >1 or knee adduction moment peak >5%, foot progression angle error, and self-reported intervention compliance) were added. WOMAC pain and functional subscores were extracted from the KOOS, rather than reporting the summary KOOS score.
6) An unplanned interim analysis was performed to evaluate MRI data quality. It was not intended to and did not impact continuation decisions or analyses in the trial.
7) We used Markov chain Monte Carlo method for Continuous Variables because this is the method most appropriate for the pattern of missing data observed in our study (i.e., missing data was arbitrary, and all outcome variables were continuous). We imputed 25 instead of 40 datasets for multiple imputation because, for the amount of missing data in our study, 20 to 24 imputations are recommended.
8) Besides the planned intent-to-treat analysis, we performed a sensitivity analysis to evaluate the effect of missing data due to the COVID-19 institutional shutdown and due to attrition.

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