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TITLE:	Biomechanical and clinical evaluation of a gait modifying device for treating knee pain
PROTOCOL NO.:	SMT202401
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Background

The initiation and progression of knee OA is influenced by many factors, including kinematics with related knee loading and increased knee adduction and flexion moments. (Zeighami et al. 2021). Most cases of OA have a clear predisposing condition, such as genetics, trauma, aging, or obesity, leading to the idea that OA describes a common endpoint with different etiologies. In any case, it is now widely accepted that OA is a dynamic and complex process, involving inflammatory, mechanical, and metabolic factors that result in the inability of the articular surface to serve its function of absorbing and distributing the mechanical load through the joint that ultimately leads to joint destruction (He et al. 2020). Joint injury alters neuromuscular control and biomechanics around the affected joint, which may contribute to cartilage degradation (Abbey et al. 2017). This tissue damage, coupled with a loss in muscle strength and degradation in neural control of the lower extremity, contribute to worsening of kinematics and joint forces. Over time, pain interferes more frequently with activities of daily living, and quality of life declines.

Kinetic variables that are associated with the development, progression, and severity of knee OA include the external knee adduction moment (KAM) and knee flexion moment (KFM) due to their correlation with a high contact force (Gupta et al. 2022). The KAM is an indirect measure of the compressive force acting on the medial compartment of the knee and the KFM an indirect measure of the lateral knee contact force acting with ambulation and can be considered a surrogate marker for the presence of knee OA (Zieghami et al. 2021). Due to the strong correlation with disease progression and pain, peak KAM during gait has become a target for treatment design with simultaneous consideration of maintaining or reducing peak KFM. One way to reduce both peak knee moment forces is to optimize one's own neuromuscular control of joint motion by altering kinematic patterns in gait (Gupta et al. 2022).

Gait modification may reduce pain and slow the progression of medial compartment knee OA (see Silva et al. 2012 for a review). Several biomechanical gait modification interventions to reduce the peak KAM have been tested. The strategies include changing medial-lateral trunk sway and changing toe-in or toe-out. Medial knee thrust, medial weight transfer and wider steps may also reduce knee load based on results of individual studies. (see Silva et al. 2012 for a review). Limitations to the translation of these methods to the general OA population include the challenges of teaching people to perform a modified walking pattern and the challenges of maintaining said gait changes during activities of daily life. It remains unclear whether these gait-retraining methods can result in lasting benefits or translate to better functionality, decreased pain, and improved quality of life. The longer-term effects are not well understood. Moreover, most of these interventions are not geared toward optimizing one's own neuromuscular control about the knee joint.

A possible method to achieve better neuromuscular control and reduce the peak KAM in people with medial compartment knee OA is to use gait-modifying shoes that create instability while walking (Drexler et al, 2012; Elbaz et al, 2010; Goryachev et al, 2011). Use of these gait-modifying shoes may effectively reduce knee pain through motor learning and adaptations in one's own neuromuscular control (Vidoni & Boyd, 2007; Orrell et al, 2006; Brooks et al, 1995).

Currently, there is only one published model of a gait-modifying shoe designed to perturb balance and reduce the KAM. The All-Phases of Step Cycle (APOS Therapy) system has

recently emerged in the scientific literature as a shoe system capable of favorably modifying gait and improving several gait parameters related to medial knee OA.

The system involves a high-cut shoe fitted with small convex rounded elements on the sole that when worn can modify knee joint loading and create instability. Instability was found to average 1.5-2.0 cm in medial, posterior, anterior and lateral directions (Goryachev et al.2010, Reichenbach et al. 2020). These elements can be shifted as needed to create more or less neuromuscular challenge and instability for the participant. This shoe design has been tested during single testing sessions (Goryachev et al. 2010), over 8 weeks (Bar-Ziv et al. 2010) over 12 weeks (Drexler et al. 2012; Elbaz et al. 2010; Goryachev et al. 2011), and over 24 weeks (Reichenbach et al. 2020).

These studies consistently indicated positive results with respect to temporal spatial gait parameters, KAM, knee pain severity, and perceived improvements in knee function. Only one of these studies addressed how pain interference from OA was altered, with results stating a mean standardized WOMAC pain score improvement from 4.3 to 1.3 in the treatment group and 4.0 to 2.6 in the control group (Reichenbach et al. 2020) However, all of these studies were conducted with support from the APOS Therapy company and may therefore be prone to reporting bias.

Deficits in the Literature:
We seek to improve upon this gait-modifying shoe concept. We will investigate our prototype gait-modifying design to determine whether differential pain and gait responsiveness to these gait-modifying shoe design occurs. We do not currently know how the motion and joint moments of the lower extremity joints above and below the knee are impacted with these types of shoes. This is an unfortunate scientific deficit because motion at the knee is controlled in part by motion at the hips and ankles. As such, we will determine how these gait-modifying shoes impact the kinematic chain. We also seek to understand how gait-modifying shoes change spatiotemporal gait metrics over time. Finally, we want to determine how the magnitude of pain relief obtained with gait-modifying shoes relates to joint mechanics and to subjective pain interference, a patient-focused outcome that represents value of the treatment. Data are scarce with respect to the acute and training-induced changes in kinematics and muscle activation that can occur with gait-modifying shoes. This study will address this deficit by examining the acute effect of wearing gait-modifying shoes and then examine the training-induced effect by having participants wear them at home and returning at 4, 8, and 12 weeks after the initial acute study.

These findings can guide us on an eventual treatment protocol and ideal follow up intervals as well as length of treatment. It is our goal to provide information to practitioners and therapists so they may use gait-modifying shoe intervention programs and treatment expectations for the population with moderate knee OA.

Purpose/Specific Aims

Determine whether patient-reported outcomes related to knee pain are improved with the use of gait-modifying shoe interventions.

Hypothesis 1: We hypothesize that participants will demonstrate lower NRSpain ratings after walking with a gait modifying shoe than at their baseline before use of device.

Determine whether these gait-modifying shoe interventions change gait parameters and compare the effectiveness over time.

Hypothesis 2: We hypothesize that the participants will change gait parameters (speed, step and stride lengths, step length symmetry, single limb support percent) while wearing the gait-modifying shoes compared to when they are not.

Criteria for Subject Selection

Number of Subjects: 15 subjects per site minimum, at a minimum of two, maximum of six sites
Gender of Subjects: Both men and women will be recruited for this study.

Age of Subjects: 40 – 85 years of age.

Race and Ethnic Origin: N/A – this study does not aim to target any particular race or ethnic origin.

Inclusion Criteria:
Male or female between 40 and 85 years of age at the time of consent
Chronic, moderate, OA-related knee pain occurring with ambulation
NRS Pain score reaches between 4/10 or greater 4+ days a week
Kellgren and Lawrence score of 2, 3 or 4, as demonstrated by x-ray within the last 2 years
Able to walk unassisted for at least 10 minutes at a time
Wear a Women's shoe size of 7 to 17 or a Men's shoe size of 5 to 15
Patient has access and ability to use a smart phone

Exclusion Criteria:
Patients diagnosed with acute septic or inflammatory arthritis
High Fall Risk (3+ falls in last year, TUG >21 seconds, TURN180 > 4 steps)
Unstable cardiovascular, orthopedic, or neurological conditions, uncontrolled diabetes, or any condition that would preclude exercise in moderate duration, moderate workload trials
Received a corticosteroid injection or invasive procedures within prior 3 months of the study
History of avascular necrosis in the knee
Experienced more than 3 falls within the last year
Pathological osteoporotic fracture
Severe symptomatic degenerative arthritis in lower limb joints other than the knees
Severe back pain, prior spinal fusion, or spinal deformity that would affect gait
Major cardiac or pulmonary conditions and any orthopedic limitation that precludes their ability to independently walk for 10 minutes or longer
Any major injury to either knee within the prior 12 months
Currently enrolled in a supervised physical therapy program
Currently using any knee brace on a regular basis for the knee pain, with the exception of basic knee sleeves
Previous partial knee joint replacement
Previous total knee joint replacement

Vulnerable Subjects: It will be emphasized that participation is voluntary. No other vulnerable populations will be considered for recruitment into this study.

Recruitment and Informed Consent:

Participants will be recruited from individual sites through corresponding physicians at outpatient clinical visits. The physicians on the protocol will ask whether the candidate is interested in hearing about this research study. If yes, the physician will then step out of the room and the study coordinator will enter the private clinical room. The study coordinator will then explain the study in detail using the informed consent document as the basis of the discussion and answer any questions from the participant. Participants can discuss it with family or support network or take the consent document home to review the information carefully. If the patient does agree to pursue the study, written signatures on the informed consent will then be obtained. The participant will be given a copy of the informed consent document after they are signed and dated. Participants are free to withdraw from the study at any time. The protocol and consent documents identify the research team's obligations to the participant and the participant's obligations to the study while he or she is a participant.

Methods and Procedures

Studies will be performed at a minimum of two, maximum of six sites. This study consists of two phases: an initial assessment and treatment visit, then periodic follow up visits for treatment adjustment and data capture. The purposes of the initial visit will be to allow the researchers to validate methodology and fine-tune the application and constitution of the gait modifying shoe soles to be used through the following 12 weeks. The initial visit will require participants to make a single visit of less than 2 hours. This will help ensure that the 12-week study is run seamlessly. The follow up visits will require participants to make three visits to the host site of less than 1 hour each. After the initial visit, the participants will be given gait-modifying shoes to wear at home and wear daily for increasing periods of time. They will be asked to record the time worn and level of pain before and afterwards on a provided paper chart for the entirety of the 12 week study. A summary of the measures used for each visit may be found in Table 1.

Table 1: Measures used for each study visit

	Initial Visit	4 Weeks	8 Weeks	12 Weeks
Health History Q	**X**	**meds only**	**meds only**	**meds only**
KOOS	**X**	**X**	**x**	**X**
Pain Body Chart	**x**			
Physical Evaluation	**X**			
Night Pain (NRSpain) & # of nights/week	**x**	**x**	**x**	**x**
Computerized Gait Recording	**x**	**X**	**x**	**X**
Video Recording	**x**	**X**	**x**	**X**
Home Walking Program	**X**	**X**	**X**	**X**

Initial Visit

After reviewing the study procedures, the therapist will aid the participants in completing a study-specific health history questionnaire that includes age, height, weight, current medical issues,

current medications and dosage, knee pain history, body diagram marking of pain locations, and the KOOS measure. The number of nights a week a patient is experiencing night pain will also be recorded along with the corresponding NRSpain rating for their night pain specifically. This information will be supplemented by medical history summaries provided by the supervising physician.

Upon completion of the questionnaires, participants will be physically assessed to characterize their tenderness to palpation, posture, joint range of motion and flexibility.

Next, participants will perform a series of gait tests which will be used to comprehensively characterize gait patterns using a computerized gait analysis system (which varies by site). These gait tests will occur while barefoot or shod with gait-modifying shoes.

Participants will be fitted with gait-modifying shoes that have an attached battery-powered pedometer for testing and to take home. The pedometer will record use on a daily basis and sync with the moveUP app on their phone during the study and will be checked periodically by study personnel via remote monitoring to measure compliance.

Walking Gait: Each participant will be fitted with a pair of gait-modifying shoes that has a modifiable element mounted to the sole of the shoe. These shoes will be worn during multiple trials of walking while their gait is recorded by a computerized gait analysis system. At the initial visit the gait-modifying shoes will first be neutrally adjusted to create the smallest amount of instability. The researcher will then iteratively adjust the placement of the modifiable element, quantifying the patients' gait pattern and asking them their immediate sense of knee pain until a suitable positioning of the elements results in enhanced gait properties and a perception of reduced pain while walking. Patients who do achieve an improved gait and reduced pain during this session will be considered to have positively responded to the gait modification therapy. Patients who are unable to achieve improved gait characteristics or a reduction in knee pain in this initial session will be considered to have not responded to the gait modification therapy. Study participation of non-responding patients will be completed at this first session, and they will not be required to continue with the home-based activities or subsequent follow-up visits.

After the initial visit, the barefoot walking analysis will be used to assess any learned changes in gait mechanics that may have resulted from therapy with the gait modifying shoes. The researcher will assess the subject's gait, and again adjust the modifiable shoe elements' placement to achieve an incremental beneficial change in the subject's gait characteristics and perceived knee pain.

Throughout the walking gait trials, a video camera will also be used to capture reference images of each of the subject's walking gait condition.

At the end of each in-person lab session, the participants will be given verbal and a paper copy of instructions for wearing and using the shoes at home. Because the use of the new shoes will either promote recruitment of different lower extremity muscles, or different activation patterns of lower extremity muscles, participants will initially wear the shoes for short periods of time. As in other training studies, it is likely that the participants will adapt to the instability of the shoes. The daily time that the participants will wear the shoe will therefore progressively increase over the

study duration. Participants will be instructed to wear the shoes and go about their daily activities using the following instructions:

- *<u>Week 1-4</u>: Wear shoes for a total of 30 minutes, of which 30%, about 10 minutes, should be spent active (walking, standing) the rest will be spent seated between bouts of activity. If walking in the shoes results in pain above what you experience when walking in regular shoes, stop wearing the shoes for the day, note the experience in the walking log. With each successive week the patient should add 10 minutes to the total amount of time in the shoes (i.e. for week 2 a total of 40 minutes in the shoes with about 12 of those minutes being active) until the total time wearing the shoes is 60 minutes per day.*

However, this recommendation can differ according to patient presentation, gait analysis results, and individual tolerance. In appropriate cases patients may be instructed to increase shoe wearing up to a maximum of 160 minutes over the course of the study. Patient shoe wearing prescription times will be recorded for each individual.

<u>Follow Up Protocol</u>

Participants will be involved in a total of four study visits at the following time points: initial, 4 weeks, 8 weeks, and 12 weeks. Participants will be asked not to start any new OA-related interventions during the 12-week period. They will also be instructed to continue with their current use of pain medications for knee pain. The number of pain medications used, both scheduled and those taken on an “as needed” basis, will be recorded during each visit. Patients can and will be seen as needed between follow up visits if problems arise with the device or pain increases.

All of the outcome measures will be taken at baseline, 4 weeks, 8 weeks, and 12 weeks except the physical evaluation. NRS_{pain} scores will also be collected weekly via the moveUP app. After the Baseline visit, shoe wearing and pain logs will be reviewed as well as documenting any changes in medication.

At the 4, 8, and 12 week visits participants will perform an instrumented gait test (same as first visit), which will be used to measure gait metrics during walking. These gait tests will occur under multiple conditions including barefoot, shod with the gait-modifying shoe, and barefoot again. At subsequent visits, the elements may be moved to improve the biomechanics of gait, to improve comfort, or to promote additional instability which may stimulate a motor-learning response. NRS_{pain} scores will be taken before and after each walking condition. High-speed video will be used to capture a video reference of each walking gait condition.

Participants will be given verbal and hard copy of updated walking prescription at each follow up. Participants will be instructed to wear the shoes and go about their daily activities indoors using the following instructions:

<u>Weeks 4-8:</u> “Wear shoes and increase your walking time up to between 15-20 minutes about 50% (40 minutes total in shoes) of the wear time per day. The walking time may be separated into two walks, if necessary. If walking in the shoes results in pain above what you experience when walking in regular shoes, stop wearing the shoes for the day, note the experience in the walking log. If a major adjustment to the element is made to alter calibration or instability for increased challenge at the 4 week follow up visit the patient may be directed to return to the initial week 1 wearing protocol.”

Weeks 8-12: "Wear shoes a total of 60 minutes per day with active time up to 50% (30 minutes), with the daily volume separated into two walks if necessary. If, at the 12 week follow up, a participant reports they are not able to walk for 30 minutes, they will be instructed to start walking for the amount tolerated and then try to increase their walks by 5 minutes each week. If walking in the shoes results in pain, reduce usage for the day and note the experience in the walking log."

Again, let it be noted that this recommendation can differ according to patient presentation, gait analysis results, and individual tolerance. In appropriate cases patients may be instructed to increase shoe wearing up to a maximum of 160 minutes over the course of the study. Patient shoe wearing prescription times will be recorded for everyone.

A deviation in the reported and the actual walking durations will be tolerated for this study since as with most exercise programs it is participant dependent, and some may acquire muscle pain and not want to walk as much the next day.

Participants will be asked to keep a log on a provided chart that will list date, start and end times, their pain level, and a description before and after wearing the shoes. The study team will contact the participant for a follow up call after week 1 and a telehealth call (video) after week 2 to see how they are doing, answer any questions and provide gentle reminders of the importance of adherence to the intervention and the tracking log. Additionally, the pedometer on one shoe will count steps and duration of use. The information from the pedometer will be downloaded between the visits and will be used to verify the self-reported compliance logs. Data collection through the app will be monitored remotely more frequently than this (checked weekly) to ensure data is being recorded and technology is working adequately. If a patient demonstrates less than 4 days a week of compliance with walking prescription, they will be contacted via phone call to determine rationale for missing days and assist in improving compliance and data collection. After 2 weeks or more of less than 4 days per week of shoe wearing the patient is criteria for removal from the study to prevent skewing of data.

Table 2: Patient Contact Time Points

Initial Visit	In person evaluation and treatment prescription
Week 1	Phone call check in
Week 2	Telehealth check in
4 Week Visit	In person re-assessment and treatment
8 Week Visit	In person re-assessment and treatment
12 Week Visit	In person re-assessment, treatment, and conclusion

*Patient contact is not limited to these time points; patients will be contacted as needed if step tracking shows lack of adherence to treatment prescription. Patients are also able to reach out to therapists as needed for any problems that arise.

Study Measures

Height and Weight: will be obtained using a standard, medical grade scale and stadiometer or via recent medical record provided by their supervising physician.

Knee Pain Assessment: The severity of knee pain while the patient stands at rest will be self-reported with the use of an 11-point numerical pain rating scale (NRS_{pain}) with anchors of 0, indicating no pain, and 10, indicating the worst possible pain. The NRS_{pain} measure is an accepted

outcome for chronic pain conditions, as described in the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (Dworkin et al. 2008). This measurement is reliable and valid for assessing pain intensity (VonKorff et al. 2000). Knee pain will be assessed after each walking condition while barefoot and wearing the shoes with elements, as well as after the functional tests. We will also use the NRS_{pain} to score each patient's night pain specifically as well as noting the number of nights per week a patient experiences instances of said pain. These pain scales will be taken with the instruction: "0 meaning you have no pain and 10 being the worst pain imaginable—you need to go to the emergency room". If a patient answers a 10 they will be asked to confirm the score with the understanding that means there is no possible way the pain they are describing could get worse. They will also mark the location of their pain on a body chart diagram.

KOOS Score: The KOOS is a self-reported outcome measure assessing the patient's opinion about the health, symptoms, and functionality of their knee (APTA, 2020). It includes 42 items in its questionnaire and has 5 subsections including: symptoms, pain, ADLs, sports/recreation, and quality of life. Each of the five scores is captured using a Likert scale with 5 answer options ranging from 0 (no problems) to 4 (extreme problems). Each subsection is calculated by the sum of the included items, which is then transformed to a 0-100 scale with zero representing severe knee problems and 100 representing no knee problems. The KOOS has demonstrated validity and reliability in patients with knee pain. It has also shown responsiveness for age and condition related subscales; for persons diagnosed with OA and the elderly being pain and ADL function respectively (Collins et. al., 2016).

Functional Mobility Tasks: Functional mobility tasks include the timed up and go and TURN180 measures which will be used as needed to determine if patients who present upon assessment with instability fall into our exclusion criteria as a fall risk. We will also utilize the instrumented gait tools to assess gait metrics and quality of movement.

Timed up and go: The patient sits in the chair with his/her back against the chair back. On the command "go", the patient rises from the chair, walks 3 meters at a comfortable and safe pace, turns, walks back to the chair and sits down. Timing begins at the instruction "go" and stops when the patient is seated.
Scores range from 1 to 5 based on the observer's perception of the patient's risk of falling (Mathias et al, 1986). Podsiadlo & Richardson, 1991, quantified the test by recommending timing (sec) the time between the command to start, till the buttocks touch the chair. The patient should have one practice trial that is not included in the score (Podsiadlo & Richardson, 1991). This test will be performed on an as needed basis as part of the exclusion criteria determination if a patient demonstrates questionable balance upon physical evaluation. Patient's taking greater than or equal to 12 seconds fall into the exclusion criteria due to increased fall risk.

Turn180: The Turn180 test is a clinically useful test of dynamic postural stability for assessing elderly people (Simpson et al., 2002). The test is part of two of the best validated clinical balance scales: the qualitative Performance-Oriented Mobility Assessment (POMA) and the Berg Balance Scale (BBS) (Netukova et al. 2024). Research indicates people who take greater than four steps to perform the turn have an increased risk of falling compared with people who take less than five

(Gamerman et al., 2019). The test is performed by asking the patient to turn in a half circle whichever direction they preferred and counting the number of steps it requires them to complete the activity. This test will be utilized on an as needed basis to rule out patients who may fall into the exclusion criteria due to increased fall risk.

Gait Assessment Systems: The system will vary by location based on what is available but will gather spatiotemporal data including at a minimum: gait velocity, single limb support percentages, step length, plantar pressure, and degree of toe-in/toe-out.

Physical Evaluation: Standard physical therapy evaluations that assesses posture, joint range of motion and flexibility that includes the items listed in Table 3, conducted at the first study visit. This assessment should take about 15 minutes. Patient will be instructed to inform the person performing the assessment of any pain that occurs throughout the testing. OAA or Orthopedic Alignment Assessment is a series of testing and observation to determine the general alignment of a person's limbs and joints. In addition to the standard evaluation outlined below the physical therapist may perform further testing techniques as the patient presentation requires. See Table 4 for special tests that may be performed as required by patient presentation in the standard evaluation.

Table 3: Physical Assessment Measures

Hip	*ROM:* IR/ER in neutral, flexion, & extension *Special Tests:* FADDIR & FABER *Strength:* flexion, abduction, adduction, TFL, & hip extension *OAA*: pelvic tilt, pelvic rotation, pelvic height, leg length, femoral torsion, femoral angle
Knee	*ROM:* flexion & extension *Special Tests:* ACL, MCL, PCL, LCL *Strength:* flexion & extension *Palpation:* medial joint line, lateral joint line, patellar borders, pes insertion, tibial tuberosity, posterior knee *OAA*: fixed flexions, hypermobility, genu varus/valgus, tibial torsions
Ankle	*ROM*: dorsiflexion & plantarflexion (active & passive) *Strength*: dorsiflexion, plantarflexion, eversion, & inversion *OAA*: hindfoot, forefoot, interaction of hindfoot/forefoot, subtalar versions
Functional Assessment	Squat & SL squat bilaterally
Balance	*Balance error score (10 sec each):* Feet together, tandem stance, single leg stance (bilaterally)
Walking Gait Analysis	Watching for gait deviations while patient walks naturally up and back in an open space (i.e. trunk lean, shortened step length, early pronation)

Table 4: Additional Special Testing

Knee	*Laxity*: Dial Test (posterolateral corner)

	Meniscus: McMurray's, Disco Test *Patella*: Clarke's test, Grind Test, Ober's Test
Hip	Hip Quadrant Testing Craig's Test
Ankle	Leeds Foot Posture Index

Pedometer: A Garmin Vivofit 4 will be attached to one of the shoes for tracking steps and duration of shoe use. The moveUP App will be installed on their Apple or Google based smart phone. The de-identified patient ID will be used as the username for the application. An email account will be needed for the data to be shared. A temporary g-mail account will be created for each participant and then deleted at the completion of the study. The participant will need to open the App at least weekly, in the vicinity of the shoes, so that the data may be synchronized. The pedometer data will be downloaded to verify compliance. Once the study is completed, the Vivofit 4 and temporary email accounts will be deactivated..

Sample Size: Power analysis was calculated using previously published data regarding differences elicited for the 11-point numerical pain rating scale (NRS_{pain}) with a rating of "0" equating to no pain and a rating of "10" to indicate the worst pain possible. It has been shown that a decrease of 2 points, or 30%, was associated with patient ratings of "much improved", and a reduction of 4 points, or 50%, was associated with patient ratings of "very much improved" (Dworkin et al. 2008). The mean score on the NRS is 5 points with a standard deviation of 2 points and the desired effect of at least 1.5 points indicates that 16 participants would be needed to have a power of 0.9 and an alpha level of 0.05. A minimum of 30 participants be enrolled in this study across the sites to ensure robust data collection.

Data Analysis and Monitoring:
Analysis for the Specific Aims:

Aim 1: Determine whether patient-reported outcomes related to knee pain are changed with the use of a gait-modifying shoe intervention.
We will use general linear modeling with repeated-measures to determine whether the numeric pain scores improved from the beginning of their initial visit to the period after each shoe trial. The between subject factor will be the time point (initial, 4 week, 8 week, 12 week) and the within-subject factor will the numeric pain scale value. Models will be co-varied by age, duration of OA symptoms, and frequency of night pain. Cohen's d values will be calculated to find the effect sizes on these variables. For these described statistical tests an α level of 0.05 will be established as significant.

Aim 2: Determine whether a gait-modifying shoe intervention changes gait parameters and to what degree over time.
Similar to Aim 1, general linear modeling with repeated-measures analysis will be used to determine whether gait measures (kinematic and kinetic scores) changed from before treatment to after the gait-modifying shoes. Specifically looking at: step length, single limb support percent, and gait speed. The between subject factor will be the before and after treatment (initial visit before treatment, after treatment), and the within-subject factor will be the time point (initial visit, 4 week, 8 week, and 12 week). Models will be co-varied by age, frequency of night pain, and duration of OA symptoms. Cohen's d values will be calculated to find the effect sizes on

these variables. For these described statistical tests an α level of 0.05 will be established as significant.

Data and Safety Monitoring Plan: Although the risk for an untoward event occurring due to participation in the study is extremely low, we will put all data safety and monitoring procedures into place. A Data and Safety Monitoring Plan (DSMP) will be implemented to ensure the safety of all participants involved in the study, and to ensure the validity and integrity of the data. The study team will monitor all aspects of safety. The Study Coordinator will meet monthly to review all Serious, Unexpected and On-site adverse events and will make recommendations to the PI and Co-investigators. Study safety personnel will be notified of all Serious and on-site events within 24 hours of initial confirmation. The PI (or study coordinator) will complete an Event notification and Evaluation form which will be reviewed by the IRB. A summary of non-serious events will be reported to the PI and IRB. A structured safety monitoring system will be established in order to assure real-time participant care and unbiased monitoring of adverse outcomes. For ongoing participant safety, events will be assessed by the PI, physician, and Co-investigators to determine if they are Serious, Unexpected or On-site, as defined below. If so, an event evaluation form will be completed that will include a description of the event, a classification of seriousness, assessment of potential relationship to the study, assessment of need for change in the consent or the study activities, a summary of known prior health issues, event outcome and a classification of the main organ system involved. The classification of potential relationship to the intervention is as follows:

Definite	Temporal pattern + Known or expected AE response pattern
Probable	Temporal pattern + Known or expected AE response pattern + Could not be explained by participant's clinical state
Possible	Temporal pattern + Known or expected AE response pattern + Could have been reproduced by a number of other factors
Unknown	Relationship for which no evaluation can be made
Not related	AE for which sufficient information exists to indicate that the cause is unrelated to the study intervention

The study PI and Co-investigators will notify the IRB of any serious adverse events that result in death or on site events that result in medical care within 24 hrs.

The study PI and Co-investigators will notify the sponsor of any serious events and the corrective action within 48 hours of occurrence. The sponsor will be notified of any non-serious events and their corrective action within 72 hours of occurrence.

Data Storage and Confidentiality:
Study data will be collected and managed using a password protected Excel spreadsheet and electronic data capture system, Greenlight Guru Clinical. Video recordings will also be securely stored in password-protected files on an encrypted USB drive and/or a computer. Data will be transferred through a password protected USB. Only de-identified data will be shared with the sponsor. The sponsor will store all the de-identified data on an encrypted password protected USB and/or a computer in password protected files that will be locked when not in use. The de-identified information may be stored, used and disclosed forever by the sponsor.

Confidentiality: Data will be used only in aggregate and no identifying characteristics of individuals will be published or presented. Confidentiality of data will be maintained by using research identification numbers that uniquely identify each individual. If walking sessions cannot

be recorded without revealing participant faces, their face will be de-identified (e.g., blurred) after recording and their participant identifier number will be utilized to label the recording. Safeguards will be established to ensure the security and privacy of participants' study records. Appropriate measures will be taken to prevent unauthorized use of study information. The research ID number will be used. The files matching participants' names and demographic information with research ID numbers will be kept in a secure and safe location at each individual site. Only authorized study team members will have access to these files.

Transition from Research Participation: N/A

Risk/Benefit Assessment

Risk Category: This study is considered to be of minimal risk to participants. While the shoe soles are engineered to create an unstable surface, the amount of instability generated is very mild, similar to walking on an uneven surface. The patient-reported outcomes measures are self-administered by the patient to determine the magnitude of benefit that the gait-modifying shoes may provide. We also limit risk by assessing balance thoroughly and excluding all participants that are not safe to partake.

Potential Risks and Protection against Risks: The risks of participating in this study are minimal. There is a risk of tripping or falling when testing or wearing the shoes. A potential discomfort may be related to wearing the shoes during testing. The shoes are purposefully designed to create a mild instability on the sole. Adjusting to the instability might initially feel uncomfortable for some people when they first wear the shoe soles. This discomfort is expected to improve over time as the participant becomes comfortable wearing them. A second anticipated discomfort is the development of mild muscle soreness in the lower extremities and lower back from wearing the shoe soles which often occurs with the start of any new therapy program where muscles engage in unaccustomed activity. This muscle soreness is transient and is expected to dissipate within 72 hours.

A possible discomfort would be knee OA-related joint pain typically experienced during walking. Just as it will occur with normal walking on any other surface, during the gait analysis, there might be minor knee joint discomfort with walking. This discomfort is transient and is expected to stop when the participant stops walking. We will have seating available in the testing area should the subject need to sit and reduce possible minor joint pain on the legs.

Although a minimal risk, completing surveys may cause stress to some participants who may believe that they are not providing correct answers to the research team. To reduce this stress, the investigators will reassure each participant that all survey answers are based on what the participant is feeling, with no “correct” answer.

Potential Benefits: There is no direct benefit to individuals participating in this study; however, study participants may gain some insight into their own gait and how knee forces may be modified to reduce OA knee pain symptoms.

Alternatives to Participation: This is not a clinical interventional study. Alternatives to participation would be to not participate. Electing not to participate will not affect the individual’s clinical care or treatment options in any way.

Subject Identification, Recruitment, and Consent/Assent

Method of Subject Identification and Recruitment: Participants will be recruited from their supervising physician at each given site during an outpatient clinical visit. In the clinic setting, physicians on the protocol will ask whether the candidate is interested in hearing about this research study. If yes, the physician will inform the study coordinator or study staff who will explain the study in detail using the informed consent document as the basis of the discussion, and answer any questions from the participant.

Process of Consent: Once a potential candidate has been identified by the physician, the physician will notify the study coordinator or study staff who will explain the study in detail using the informed consent document as the basis of the discussion and answer any questions from the participant. Prospective participants can discuss it with their family or support network or they can take the consent document home to review the information. If the patient does agree to pursue the study, written signatures on the informed consent form will then be obtained. The participant will be given a copy of the signed informed consent document. Participants are free to withdraw from the study at any time. Should a patient choose to not participate or withdraw from the study, their clinical care will not be affected in any way.

Subject Capacity: All prospective participants must have the ability and capacity to provide written, informed consent to participate in this study.

Subject/Representative Comprehension: The study coordinator or study staff will review the study in detail with prospective participants. Candidates will be encouraged to ask questions throughout the consent process. They will be given the option to take the consent form home and discuss it with family, or other support network, prior to signing the informed consent document.

Debriefing Procedures: N/A

Documentation of Consent: All signed informed consent documents will be kept at the in a secure location.

Costs to the Subject: There will be no costs to the subjects for participating in this study.

Payment for Participation: The participants in this study are partners in this research. They will not be compensated monetarily for participation.

Conflict of Interest: None.

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