Wearable sensor-based Outcomes Following Physical Therapy in Knee Osteoarthritis: A Feasibility Study (WESENS-OA)

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Table of Contents

1. STUDY SUMMARY

1.1. Synopsis

This will be a longitudinal, single arm, 19-week study to investigate the utility of digital assessments to measure the efficacy of physical therapy (PT) for reducing pain and improving function in people with knee osteoarthritis (OA).

A total of 60 participants will be included. Participants will receive a supervised exercise-based PT for 12 weeks and will undergo multiple assessments of strength, balance, gait and joint movement while being monitored with a motion capture system and wrist and lumbar wearable sensors. Additionally, participants' activities will be monitored in the real world with the same wrist and lumbar wearable sensors. After completion of the PT program, participants will be monitored for an additional 6-week period to measure persistence of treatment effect. During that time, they will continue to follow an exercise program at home.

The primary objective will be to measure the effect of PT on functional performance and pain reduction using both patient reported outcomes questionnaires (PROs) and digital metrics obtained from the laboratory assessments and wearable sensors worn in the real world. Pain phenotyping questionnaires and quantitative sensory testing assessments will also be used to evaluate the effect of specific pain phenotypes in treatment response.

A substudy will be undertaken to assess reproducibility of sensor-based measures during physical performance testing across at-home and in-lab implementation, as well as, reproducibility of these measures over repeated at-home implementation.

1.2. Schedule of Activities

Table 1: Schedule of Activities

Week		-4 to -2		-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	ET	Time (min)
Visit		SV1 (online)	SV2 (phone)	BL+SV3						W6						W12						W18			
Review Eligibility		x	x	x																					
Consent				x																					
QUESTIONNAIRES																									
DSIS				DAILY																					2-3
Past-day medication use				DAILY																					
KOOS (Pain, ADL)				x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
NRSna				x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	1
PGA-OA				x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	1
Treatment History				x						x						x						x		x	
Pain Survey	WPI			x						x						x						x		x	
	Catastrophizing			x						x						x						x		x	
	Homunculus			x						x						x						x		x	
	painDETECT©			x						x						x						x		x	
KOOS (Symptoms, S/R, QOL)				x						x						x						x		x	
Demographics				x																					1-2
Comorbidities				x																					4-5
MOEES				x																					3-4
MPDQ				x																					4-5
CES-D				x																					2-3
Exit Survey	Effect of PT Anchor Question																					x		x	
	Feedback on study																					x		x	
	Sensor comfort																					x		x	
VITALS, WEIGHT, AND PHYSICAL PERFORMANCE TESTS																									
Vitals†				x						x						x						x		x	
Height†				x																					
Weight†				x						x						x						x		x	
Medicines past 48 hrs				x						x						x						x		x	

7-meter gait test*§			x					x						x						x		x	
15s Step-up Test (right and left)*§			x					x						x						x		x	
6MWT*†			x					x						x						x		x	
SCT*†			x					x						x						x		x	
Modified SPPB*#§			x					x						x						x		x	
Strength Testing†			x											x								x	
3D OPTICAL MOTION CAPTURE AND EMG TESTS																							
Walk at self-selected pace**†			x											x								x	
Walk at fast pace**†			x											x								x	
Sit to stand**†			x											x								x	
~~Stair ascent & descent**†~~			*											*								*	
Balance**†			x											x								x	
QUANTITATIVE SENSORY TESTING AND EXERCISE-INDUCED HYPOALGESA																							
QST PPT†			x											x								x	
QST TS†			x											x								x	
QST CPM†			x											x								x	
EIH†			x											x								x	
PLACEMENT OF AT-HOME WEARABLE SENSORS																							
Lumbar-Worn Sensor (Axivity)			x					x						x						x		x	
Wrist-Worn Sensor (Actigraph)			x																				
USE OF 3-SENSOR IMU SYSTEM§																							
3-sensor IMU system			x					x						x						x			
INTERVENTION																							
PT				x	x	x	x	x	x	x	x	x	x	x									
OTHER DOCUMENTATION																							
AE/SAE			AS NEEDED																				
Protocol Deviation			AS NEEDED																				

† denotes that these tasks will not be performed if in-lab visit is not possible
**denotes that these tasks will be performed while wearing lumbar sensors, wrist sensors, and 8-sensors IMU system*
*** denotes that these tasks will be performed while wearing lumbar sensors, wrist sensors, 8-sensors IMU system, optical motion capture markers, and EMG sensors*
§denotes that these tests will be administered at-home while wearing lumbar sensor, wrist sensor, and 3-sensor IMU system, only if in-lab visits are not possible
#denotes that balance component of this test will not be performed if administered at-home
ET = early termination visit

2. INTRODUCTION

Current evidence indicates that PT interventions can reduce pain and improve function in people with knee OA. PT may result in improvement by several mechanisms including decreasing knee joint load, altering lower limb alignment, improving range of motion and restoring neuromuscular function (Page et al, 2011), thereby allowing people with knee OA who have been previously inactive due to their pain to participate in greater volume and intensity of activity. Increased activity has its own benefits in terms of improved fitness and quality of life, however, the type of activity and the nature of mechanical loading in joints that have been underutilized due to chronic pain may, in part, determine whether that change is productive or detrimental to joint health. Therefore, improved joint mechanics and kinematics may reduce the risk of negative outcomes such as rapidly progressing joint degeneration or outright injury potentially caused by increased activity in a previously underutilized joint.

2.1. Study Rationale

This study will begin to address the hypothesis that PT may reduce the risk of joint injury that may accompany pain relief by determining if we can use digital tools to measure improved physical function after a specific PT program designed for people with knee OA. Outcomes will be measured during regular in-lab assessments and during analysis of unscripted activity and performance metrics in the real world. Several associated questions will be addressed including 1) does PT reduce pain and improve function in people with OA of the knee? 2) can such improvement be objectively

measured with wearable sensors in a non-controlled environment (i.e., participants' daily activities in their natural environments)? 3) does pain phenotype influence response to PT? 4) does pain catastrophizing lead to poorer response to physical therapy?

2.2. Background

OA is characterized by pathologic lesions of numerous tissues within the joint, leading to chronic pain and loss of function primarily involving the knee and hip joints and affecting 10% of men and 18% of women older than 60 years. Moreover, increases in life expectancy and ageing populations are expected to make OA the fourth leading cause of disability by 2020 (Woolf et al, 2003). Previous studies have attested the benefit of exercise in the management of OA, with demonstrated improvements in pain, physical function and quality of life (Goh et al, 2019; Ferreira et al, 2015). Furthermore, resistance training programs have been shown to improve gait velocity and muscle strength. However, its efficacy significantly varies across patients and there is an unmet need to understand the physiological and biomechanical factors underlying the equation. For instance, the degree of knee alignment was found to represent a local mechanical factor that can mediate symptomatic outcomes from exercise in osteoarthritis of the knee (Lim et al, 2008), raising the need to develop more individualized therapeutic interventions for people with OA.

Technological advances in multimodal wearable sensors are increasingly allowing the measurement of human activity and physiological data in real time in natural environments both in healthy individuals and in disease states. For instance, gait speed measured by a wearable monitor and motion parameters derived from 3D inertial sensors applied to the lumbar area have been shown to distinguish between participants with OA and healthy controls (Sparkes et al, 2019; Bolink et al, 2012). Such novel digital approaches therefore hold great promise to improve the precision, accuracy, and reliability of clinical endpoints. However, additional work is still needed to validate and develop algorithms that may in the future be used to monitor treatment response in patients with OA using wearable sensors. The ability to obtain pertinent information from wearable sensors would overcome the burdensome and costly assessments in a formal gait laboratory, enabling clinicians to feasibly assess key aspects of their patients' response to therapy and modifying care as needed if signals concerning potential adverse effects on the joint are detected.

This study will provide critical understanding on the feasibility, usability, and applicability of the selected wearable sensors and monitoring devices in the assessments of functional measures, extracting features that are intended to be relevant to the development of functional endpoints in people with knee OA, as determined by physical performance measurements both in-lab and in the real world.

2.3. Benefit/Risk Assessment

Participants may benefit from receiving PT as it is currently standard of care for management of OA of the knee, and generally recommended as first-line therapy for all patients with knee OA. No other personal benefits are expected from participating in this study. The information collected in this study will be useful in developing better ways to assess the impact of exercise and strength therapy in knee OA. Hence, the overall goal is to improve the quality of information available to physicians treating patients with knee OA and to researchers developing new therapies for OA.

Intervention risks: In some persons, knee pain could worsen with exercise. To reduce this risk, participants will receive a supervised and standardized knee OA specific exercise protocol, with individualized progression across participants by a physical therapist member of the study team.

Wearable sensor risks: There is the possibility of skin irritation and discomfort with continued wearable device use. In case of discomfort or skin irritation, participants will be instructed to remove the device on their own.

Motion analysis risks: There are no known side effects from being filmed by high speed cameras. Since the participants will be asked to perform walking, stair climbing type activities, as with any such activity, there is a risk that they may lose balance, stumble, fall, and experience an injury. There is a risk of slight discomfort with the skin shaving and cleaning with the alcohol swab before placing the EMG sensors. All participants will observe a demonstration of the movement and will be able to perform a few practice trials to become familiar with each activity prior to data collection. The testing area will be well lit and clear of any obstacles. The participants will be provided ample rest breaks. They will be encouraged to perform each activity at a rate that they feel comfortable. If they show signs of shortness of breath, testing will be stopped immediately, and they will be allowed to rest. The participants will be explained the process of placing the EMG sensors. If a participant expresses discomfort with the shaving or cleaning, the process will be stopped and the sensors will be placed without the skin preparation.

Strength and functional testing risks: Some soreness can be present immediately after or the next day after performing maximal force contractions during the strength testing. Since the participants will be asked to perform walking, stair climbing type activities, as with any such activity, there is a risk that they may lose balance, stumble, fall, and experience an injury. All participants will be made aware of this, provided adequate rest between contractions, and advised to apply ice to involved muscle groups in case of soreness. To minimize the risk of falling during each of the typical daily activities that the participant will perform (walking, stair climbing, and getting up from a chair), the participant will first observe a demonstration of each activity and will be able to perform a few practice trials to become familiar with each activity prior to data collection. The testing area will be well lit and clear of any obstacles, and a member of the study team may accompany the participant during these activities to assist in guarding against falling. During stair climbing activities, the participant will also be allowed to use the staircase handrails for support.

Questionnaire risks: The questionnaires to be administered are generally about pain and function, similar to what patients experience during a routine clinical examination. The participants may feel emotional or upset when answering some of the questions in the questionnaires. Participants do not have to answer any questions that make them feel uncomfortable.

Quantitative Sensory Testing (QST) risks: These tests are generally well-tolerated, but it is possible that the algometer and temporal summation probes may cause discomfort. The principal investigators have extensive experience with these protocols, having assessed these tests in ~3000 older adults in 4 consecutive study visits without any issues or complaints. In rare instances, the probes may cause skin irritation. Application of the blood pressure cuff will cause decreased blood flow to the hand, which may cause pain or tissue damage; the cuff inflation is limited to no more than 5 minutes for safety reasons. To minimize the risk of tissue damage, blood pressure cuff inflation will not be performed in participants who self-report a myocardial infarction within the past year, a history of Raynaud's syndrome or disease, active vasculitis, or severe peripheral vascular disease. The test will be stopped if any abnormal symptoms occur, including bruising or bleeding occur, or at participant request. A trained study staff member will start with the lowest weight probe and progress stepwise to probes of greater weight until the participant reports a pain rating of 3-4 out of 10 (where 10 would be the worst pain the participant can imagine). For the pressure algometer, pressure is applied at a steady state until the pressure first changes to slight pain. The pressures used in this study and the length of time the probes are touched to the skin have been used safely in other studies, including those of participants with chronic pain.

COVID risks: Traveling to study visits and going into the clinic and lab at Boston University increase participant's potential exposure to COVID. In addition to BU mandated risk mitigation protocols at the lab and clinic, participants will be offered cab fare to commute for their in-lab or in-clinic visits.

Unknown risks: This study may include risks that are unknown at this time. Throughout the study, the researchers will notify the participants of new information that may become available and might affect the decision to remain in the study. This includes, but is not limited to, information that may affect their safety, well-being or medical care.

Loss of Confidentiality: The main risk of allowing us to use and store participant information for research is a potential loss of privacy. We will implement standard best-practices for ensuring privacy and data confidentiality, including secure databases, secure storage of the master key with access only by the PIs and project manager.

3. OBJECTIVES, AIMS, AND ENDPOINTS

Objectives

1. Demonstrate the benefit of knee OA-specific PT on participant pain and function
2. Develop sensor-based measures of gait and functional performance
3. Demonstrate impact of PT on real world participant activities and performance

	Aim(s)	**Endpoints**
Primary	1. Measure the effect of PT on functional performance using digital measures from wearable sensors	• Sensor metrics obtained during functional performance tests in-lab, such as gait (e.g. gait speed; stride velocity) and sit to stand (e.g., time taken) • Wearable sensor metrics obtained from real world (at-home) data (e.g. steps per day and sleep duration)
Secondary	1. Compare in-lab and real world (at-home) sensor metrics with ePRO outcomes 2. Assess the effect of PT on sleep using ePRO (DSIS questionnaire) and wearable sensor metrics 3. Assess the persistence of the PT effect from week 12 to week 18 using in-lab and real world (at-home) sensor metrics, and ePROs	• KOOS pain, symptom, ADL scores, and PGA score • Sensor metrics obtained from in-lab assessments (e.g. gait speed, stride velocity and sway) • Sensor metrics obtained from real world (at-home) data (e.g. steps per day) • DSIS score • Sleep metrics obtained from wearable sensors
Exploratory	1. Assess whether sensor-based baseline measures can stratify treatment response 2. Assess whether participant phenotype; pain, function, affective traits (catastrophizing), can stratify treatment response	• In-lab pain phenotype assays: quantitative sensory testing measures including temporal summation, conditioned pain modulation and exercise-induced hypoalgesia • Responses from questionnaires for pain phenotyping: PainDETECT© questionnaire scores; Body & Joint Pain Homunculus and Pain Catastrophizing scale Outcomes

		• Outcome expectation from exercise at baseline: Total MOEES score
Substudy	1. Examine the test-retest reliability of at-home instrumented physical performance tests 2. Examine agreement between wearable sensor data collected during in-lab and at-home instrumented physical performance tests	• Sensor metrics obtained during functional performance tests in-lab, such as gait (e.g. gait speed; stride velocity) and sit-to-stand (e.g., time taken)

4. STUDY DESIGN

4.1. Overall Study Design

Participants with baseline pain during weight-bearing activities due to their knee OA will be recruited to a 19-week study. Eligible participants will be assessed at baseline and will undergo a supervised exercise-based PT program for 12 weeks as well as multiple in-lab functional assessments of strength, balance, pain, and gait while being monitored with an optical motion capture system, inertial motion capture system, surface EMG, and two wearable sensors at the wrist and lumbar areas (Actigraph and Axivity, respectively). Additional study visits will occur at week 6 and week 12 (end of PT). Participants' activities will be continuously monitored in the real world with the wrist sensor for the total duration of the study and for week-long periods with the lumbar sensor. There will be an additional 6-week monitoring period to measure persistence of treatment effect (i.e., week 12 to 18). The final in-lab visit will occur at the end of 18-weeks and the final at-home assessment with the lumbar and wrist sensors will occur in week 19. In case, in-lab visits are not possible due to COVID-19, a modified protocol will be used to collect outcomes remotely.

4.2. Sample Size Calculation

The sample size calculation for this study was based on the traditional primary outcome for OA studies, i.e. the WOMAC pain and function scores. A successful digital endpoint can detect changes with treatment with a smaller sample size than the WOMAC. Meta-analyses of published RCTs on land-based therapeutic exercise compared with a non-exercise control report (Fransen et al, 2015) an effect size of 0.49 (95%CI 0.39-0.59) for improvements in pain immediately post-treatment and an effect size of 0.52 (95%CI 0.39-0.64) for improvements in function immediately post-treatment. To account for potential differences in study populations and intervention protocols, we used conservative effect sizes of 0.40 for both pain and function outcomes. Given this effect size, assuming a significance level of 0.05 with a two-tailed distribution and power of 80%, the total sample size estimated for a paired t-test analysis is 52 for a single-arm study. Accounting for an expected 10% attrition, we would need 57 participants. Hence, the proposed sample size of 60 should be sufficient to detect significant changes in the WOMAC scores (traditional primary outcomes).

5. STUDY POPULATION

The target population will be people with pain due to knee osteoarthritis.

5.1. Inclusion Criteria

- Male or female of any race, ≥ 50 years of age.
- A confirmed clinical diagnosis of osteoarthritis of the knee based on American College of Rheumatology criteria (confirmed by the participants' attending physician).

- Score ≥ 3 on weight-bearing questions from the Knee injury and Osteoarthritis Outcome Score (KOOS) Pain Subscale in the index knee
- BMI ≤ 40 kg/m^2
- Able to walk without assisted devices (eg, cane or walker) for at least 20 minutes
- Can speak and understand English at a sufficient level to understand the study procedures and informed consent.
- Available for the study duration

5.2. Exclusion Criteria

- Contraindication to exercise
- Other pain in lower back or legs that is greater than knee pain
- Currently receiving chemotherapy or radiation therapy for cancer except non-melanoma skin cancer
- History of other disease that may involve the index joint including inflammatory joint disease such as rheumatoid arthritis, seronegative spondyloarthropathy (eg, ankylosing spondylitis, psoriatic arthritis, inflammatory bowel disease related arthropathy), crystalline disease (eg, gout or pseudogout), lupus erythematosus, knee joint infections, Paget's disease affecting the knee, or knee joint tumors.
- Any knee surgery in the previous 6 months
- Joint replacement in either hip or ankle
- Previous knee osteotomy partial or total knee replacement in either knee
- Planned major treatment for knee OA (e.g., surgery, injections, physical therapy) during the study period
- Planned major surgery in the next 6 months
- Corticosteroid or hyaluronic acid injections in either knee in the previous 3 months
- Neurological conditions that impacts motor functioning (e.g., stroke, Parkinson's disease, Alzheimer's disease, Multiple Sclerosis, diabetic neuropathy, etc).
- Pregnancy (self-report)
- Received physical therapy for knee OA within past 6 months
- Known or suspected non-compliance, drug or alcohol abuse
- Participation in another clinical trial for treatment of any joint or muscle pain
- Participants who are investigational site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the Investigators.

5.3. Additional Considerations

The use of medications for acute or chronic pain management will not be used as an exclusion criteria, however we will monitor its use throughout the study's duration. Participant medication use will be recorded at every lab visit and every PT visit. Additionally, participants will complete a weekly medication report ePRO.

6. STUDY INTERVENTION AND ASSESSMENTS

6a. MAIN STUDY

Recruitment and screening:

Participants will be recruited through multiple channels (flyers, newspaper advertisements, clinical data warehouse, etc.) including via social media using Trialfacts. Screening will occur via a 4-step process. Step 1 will be online pre-

screening using Trialfacts screening webpage. Those eligible will then undergo telephone pre-screening as step 2. Step 3 would be obtaining confirmation of knee OA diagnosis from the participant's physician along with clearance to participate in an exercise program. Step 4 will be an in-lab visit (part of baseline visit) to confirm BMI eligibility. If in-lab screening visit is not possible due to COVID-19, BMI eligibility will be determined from the physician diagnosis letter that includes a most recent height and weight.

COVID-19 Screening: Prior to all in-lab and in-clinic visits, participants will be screened for potential exposure to COVID-19 using BU mandated protocols. Participants will be called prior to their visit to determine if they have any COVID-19 related symptoms, if they have been in close contact with a known or suspected COVID-19 positive case, request they take their temperature prior to their appointment, and inform participants to call the lab/clinic if they develop and COVID related symptoms prior to their visit. In addition, participants will undergo symptom and temperature screen in person when they arrive for lab/clinic visits. Participants will be required to wear a face mask during the entire visit and perform hand hygiene before entering the lab. This screening will remain in place until Boston University guidelines recommend discontinuation of its use.

Informed consent: Most participant consents will be completed in-person during the baseline in-lab visit. For participants in the substudy randomized to completing the baseline at-home visit prior to the baseline in-lab visit (n=6-10), the informed consent will be obtained during an additional in-lab visit specifically for BMI screening, obtaining consent and providing tablet computer and sensors. If the in-lab visit is not possible due to COVID-19 related restrictions, the informed consent will be obtained remotely via REDCap and video call.

Intervention: The intervention will consist of an exercise-based physical therapy program for 12 weeks. The intervention will also include pain education and manual therapy as needed. There will be two visits per week for the first 6 weeks and one visit per week for the next 6 weeks. The table below shows which visits will be in-clinic (IC) vs. tele-health (TH) and clinical assessments during the intervention. After completing the PT program, participants will follow an exercise plan at home from week 13 to 18.

If in-clinic intervention visits are not possible due to closure of the BU Physical Therapy Center for reasons related to COVID-19, they will be delivered via tele-health. However, the first physical therapy intervention visit will always be in-clinic.

Week	**1**	**1**	**2**	**2**	**3**	**3**	**4**	**4**	**5**	**5**	**6**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Intervention Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Visit Type	IC	IC	IC	IC	TH	TH	TH	TH	IC	IC	IC	IC	TH	TH	IC	TH	TH	IC
QUESTIONNAIRES																		
Exercise Adherence	DAILY																	
KOOS	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Pain (current, best, worst)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
NPQ	x											x						x
GROC												x						x
Modified STarT Back	x																	
CSI	x																	
IPAQ	x																	
WAI			x															
CLINICAL ASSESSMENTS																		
Alignment	x	As needed																
Gait	x	As needed																
TUG	x	As needed																

Single Limb Balance	x	As needed
Step performance	x	As needed
Sit to stand/squat performance	x	As needed
ROM	x	As needed
Joint Play	x	As needed
MMT	x	As needed
Muscle Length	x	As needed

Assessments: Participants will be asked to participate in 4 (four) laboratory assessments; 4 (four) week-long monitoring periods with a lumbar sensor throughout the study; and continuous monitoring with a wrist sensor throughout the study's duration. Additionally, participants will complete daily questionnaires (sleep interference, medication use, exercise and activity log) and weekly questionnaires for assessment of pain and physical function (ie, KOOS [pain and symptoms], PGA-OA, NRSna).

Visit #1 (Baseline Assessment; Week -1)

Participants will complete questionnaires (see table above) and undergo multiple assessments of gait, strength and function in the lab.

Measurements of vital signs (heart rate, blood pressure) will be performed including measurement of height and weight. If the baseline visit occurs at-home due to COVID restrictions vitals, height, and weight will not be performed.

The wrist sensor will be worn on the non-dominant wrist until the end of the study at week 18. The lumbar sensor will be used for a week-long period and subsequently removed by the participants at home and mailed back to the site.

This visit will include physical performance tests (6-minute walk test, stair climbing test, 7-meter gait test, modified short-performance physical battery, and a 15 second step-up test). All of these tests will be done with the lumbar sensor, 8-sensor inertial system, and wrist sensor worn by the participant. In case this visit is done at-home, 6-minute walk test, stair climbing test, and balance and gait portion of modified short-performance physical battery will not be done. For the at-home visit, the tablet computer, a 3-sensor inertial system (both feet and trunk), lumbar sensor, and wrist sensor will be mailed to the participants ahead of time with detailed written and video instructions. Participants then will be instructed via live video calls on how to set-up and use these devices and also collect data for the baseline visit. An initial phone call may be used to help participants become familiar with Zoom.

Pain in the index knee will be assessed on a numeric rating scale (ranging from 0=*No pain at all*, to 10=*Worst imaginable pain*) at the start and end of the session. In addition, multiple patient-reported outcomes will be collected (see Table earlier).

Participants will undergo 3-D optical motion capture assessment during walking at self-selected pace, walking at fast pace, , getting up from a chair, and standing balance. The participants will be instrumented with lumbar sensor, 8-sensor inertial system, wrist sensor, optical motion capture sensors, and surface electromyography sensors. These tests will not be performed in at-home visit.

Participants will undergo assessment of strength in the quadriceps and hamstring muscles. These tests will not be performed in at-home visit.

Participants will also undergo Quantitative Sensory Testing (including an assessment of Exercise-Induced Hypoalgesia) for pain phenotyping. These tests will not be performed in a at-home visit.

This visit is expected to last approximately 4 hours 30 minutes if performed in-lab. This visit is expected to last approximately 1 hr 30 minutes if performed at-home.

Visit #2 (Week 6)

Participants will complete questionnaires (see table above) and undergo multiple assessments of function in the lab.

Measurements of vital signs (heart rate, blood pressure) and weight will be performed at the beginning of the visit. If this visit occurs at-home due to COVID restrictions vitals and weight will not be performed.

Participants will continue to use the wrist sensor at home. The lumbar sensor will be used for a week-long period and subsequently removed by the participants at home and mailed back to the site.

This visit will include physical performance tests (6-minute walk test, stair climbing test, 7-meter gait test, modified short-performance physical battery, and a 15 second step-up test). All of these tests will be done with the lumbar sensor, 8-sensor inertial system, and wrist sensor worn by the participant. In case this visit is done at-home, 6-minute walk test, stair climbing test, and balance and gait portion of modified short-performance physical battery will not be done. For the at-home visit, the 3-sensor inertial system (both feet and trunk) and lumbar sensor will be provided to the participants ahead of time with detailed written and video instructions. Participants then will be instructed via live video calls on how to set-up and use these devices and also collect data for the second visit.

Pain in the index knee will be assessed on a numeric rating scale (ranging from 0=*No pain at all*, to 10=*Worst imaginable pain*) at the start and end of the session. In addition, multiple patient-reported outcomes will be collected (see Table earlier).

This visit is expected to last approximately 1 hour if performed in-lab. This visit is expected to last approximately 1 hr if performed at-home.

Visit #3 (Week 12)

Participants will complete questionnaires (see table above) and undergo multiple assessments of gait, strength, and function in the lab.

Measurements of vital signs (heart rate, blood pressure) and weight will be performed at the beginning of the visit. If this visit occurs at-home due to COVID restrictions vitals and weight will not be performed.

Participants will continue to use the wrist sensor at home. The lumbar sensor will be used for a week-long period and subsequently removed by the participants at home and mailed back to the site.

This visit will include physical performance tests (6-minute walk test, stair climbing test, 7-meter gait test, modified short-performance physical battery, and a 15 second step-up test). All of these tests will be done with the lumbar sensor, 8-sensor inertial system, and wrist sensor worn by the participant. In case this visit is done at-home, 6-minute walk test, stair climbing test, and balance and gait portion of modified short-performance physical battery will not be done. For the at-home visit, the 3-sensor inertial system (both feet and trunk) and lumbar sensor will be provided to the participants ahead of time with detailed written and video instructions. Participants then will be instructed via live video calls on how to set-up and use these devices and also collect data for the third visit.

Pain in the index knee will be assessed on a numeric rating scale (ranging from 0=*No pain at all*, to 10=*Worst imaginable pain*) at the start and end of the session. In addition, multiple patient-reported outcomes will be collected (see Table earlier).

Participants will undergo 3-D optical motion capture assessment during walking at self-selected pace, walking at fast pace, , getting up from a chair, and standing balance. The participants will be instrumented with lumbar sensor, 8-sensor

inertial system, wrist sensor, optical motion capture sensors, and surface electromyography sensors. These tests will not be performed in at-home visit.

Participants will undergo assessment of strength in the quadriceps and hamstring muscles. These tests will not be performed in at-home visit.

Participants will also undergo Quantitative Sensory Testing (including an assessment of Exercise-Induced Hypoalgesia) for pain phenotyping. These tests will not be performed in a at-home visit.

This visit is expected to last approximately 4 hours and 30 minutes if performed in-lab. This visit is expected to last approximately 1 hour if performed at-home.

Visit #4 (Week 18)

This will be the final laboratory visit. Participants will complete questionnaires (see table above) and undergo multiple assessments of gait, strength, and function in the lab.

Measurements of vital signs (heart rate, blood pressure) and weight will be performed at the beginning of the visit. If this visit occurs at-home due to COVID restrictions vitals and weight will not be performed.

Participants will continue to use the wrist sensor at home. The lumbar sensor will be used for a week-long period and subsequently removed by the participants at home and mailed back to the site.

This visit will include physical performance tests (6-minute walk test, stair climbing test, 7-meter gait test, modified short-performance physical battery, and a 15 second step-up test). All of these tests will be done with the lumbar sensor, 8-sensor inertial system, and wrist sensor worn by the participant. In case this visit is done at-home, 6-minute walk test, stair climbing test, and balance and gait portion of modified short-performance physical battery will not be done. For the at-home visit, the 3-sensor inertial system (both feet and trunk) and lumbar sensor will be provided to the participants ahead of time with detailed written and video instructions. Participants then will be instructed via live video calls on how to set-up and use these devices and also collect data for the fourth visit.

Pain in the index knee will be assessed on a numeric rating scale (ranging from 0=*No pain at all*, to 10=*Worst imaginable pain*) at the start and end of the session. In addition, multiple patient-reported outcomes will be collected (see Table earlier).

Participants will undergo 3-D optical motion capture assessment during walking at self-selected pace, walking at fast pace, getting up from a chair, and standing balance. The participants will be instrumented with lumbar sensor, 8-sensor inertial system, wrist sensor, optical motion capture sensors, and surface electromyography sensors. These tests will not be performed in at-home visit.

Participants will undergo assessment of strength in the quadriceps and hamstring muscles. These tests will not be performed in at-home visit.

After the final visit participants will wear the wrist and lumbar sensor for the final week-long wearable monitoring period and mail the sensors back to the lab after the final week. This visit is expected to last approximately 4 hours and 30 minutes if performed in-lab. This visit is expected to last approximately 1 hour if performed at-home.

6a. SUBSTUDY

All participants will be asked to participate in the substudy until the enrolment targets for the substudy are met. The aims of the sub-study are to:

1. Examine the test-retest reliability of at-home instrumented physical performance tests

2. Examine agreement between wearable sensor data collected during in-lab and at-home physical performance tests

Participants will be wearing a 3-sensor inertial system in addition to the lumbar sensor.

Recruitment and screening: Participants from the parent study who are able to attend a baseline visit in-lab will be asked to participate in the substudy, for up to a total sample size of 20.

Substudy sample size: The size of the substudy was based on data collected from a group of healthy adults (n=32, [65-85] years old). Test-retest reliability of gait metrics between two lab visits derived from lumbar sensor data using the GaitPy algorithm (Czech et al., 2019) and calculated using the intraclass correlation coefficient (ICC) was 0.85 [0.71 0.92] for gait speed. To be able to replicate these substantial ICC values between two at-home assessments, we estimate that we need at least 11 participants (based on ICC H_0 of 0.42 computed by generating a null distribution based on 10,000 permutations of the gait speed across subjects between visit 1 and visit 2 and taking the 99th percentile of this distribution as ICC H_0; an ICC of 0.85, and using a one-tailed test with alpha=0.05 and power=0.8; Computed using R package ICC.Sample.Size; Zou, 2012).

Considering 10% attrition, we estimate that 12 participants are required for this substudy.

We will undertake interim analysis after 12 participants have completed the substudy (while continuing to enroll) to determine if additional participants are required to address the aims of this substudy.

Assessments: Participants will be asked to participate in 2 assessments of which 1 will be in-lab and 1 will be at-home. The order of these assessments will be randomized and occur within 2-weeks of each other.

At-home Visit

Participants will be provided hardware including 3-sensor inertial system and lumbar sensor with detailed written and video instructions. Participants will also be provided with cones connected with a string that is 7-meters long for the gait test, a chair for the sit-to-stand tests, and a step-up box for the step-up tests. A tele-research visit will be scheduled during which the researchers will guide the participants through application of all sensors and the tests. Physical performance tests will include 7-meter gait test, 5 times sit to stand test (collected as part of the modified short-performance physical battery), and 15 second step-up test. All of these tests will be done with the lumbar sensor, 3-sensor inertial system, and wrist sensor worn by the participant. After the tests are complete the participants will be asked to remove all sensors and wait for 15-minutes during which time they may be asked to complete questionnaires described elsewhere. After 15-minutes, the participants will re-place all of the sensors and repeat all the activities. At the end of the tele-research visit, participants will be guided into removing the sensors and mail it back to the research team. The lumbar sensor may be kept on depending on whether the participants have already completed the in-person visit or not.

In-lab visit:

This is the same as the baseline visit in the parent study.

6.1 Activities/Assessments and Associated Endpoints

6.1.1 In-Lab Gait, Strength, and Functional Assessments

3D Motion Capture Assessment

Participants will perform specific tasks while being monitored with a 3D motion capture system, wrist and lumbar wearable sensors, and surface electromyography (EMG) sensors. For 3D tracking, small plastic lightweight markers will be placed (14 mm in diameter) on the legs and trunk. These markers are covered in retro-reflective tape and can be detected by the optical motion capture cameras. Surface electromyography (EMG) sensors will be placed on vastus lateralis, vastus medialis, medial hamstrings, lateral hamstrings, medial gastrocnemius, and lateral gastrocnemius muscles after cleaning and shaving the skin. The tasks to be performed include (a) walking at self-selected speed (4-12 trials), (b) walking at fast speed (4-12 trials), (c) sit to stand (4 trials), and (d) standing with eyes open and eyes closed (two 30 second trials in each condition). Practice trials are performed prior to each task.

Devices to be used: Qualisys cameras, Sony video camera, AMTI force plate, AMTI staircase, Delsys EMG

Raw Data obtained:

- Ground reaction force (x, y, z)
- Marker trajectories (x, y, z)
- Raw electromyogram (various muscles – VM, VL, MH, LH, MG, LG)

Derived measures:

Gait Measures
Cadence (steps/min)
Step length symmetry
Gait speed (m/s)
Stride duration (s)
Stride duration asymmetry (s)
Step duration (s)
Step duration asymmetry (s)
Initial double support time (s)
Terminal double support time(s)
Total double support time (s)
Single limb support time (s)
Stance time (s)
Swing time (s)
Step length (m)
Peak knee index (%BodyWeight x Height
Knee flexion excursion (deg)
Knee extension excursion (deg)
Peak medial quadriceps-medial hamstrings co-contraction during loading response during walking at self-selected pace
Peak lateral quadriceps-lateral hamstrings co-contraction during loading response during walking at self-selected pace
Peak sagittal trunk angle (deg)
Peak knee adduction moment (%BodyWeight x Height)
Peak knee flexion moment (%BodyWeight x Height)
Knee adduction moment impulse (%BodyWeight x Height x Sec)
Knee flexion moment impulse (%BodyWeight x Height x Sec)
Peak sagittal total support moment (%BodyWeight x Height)
Sit-to-stand measures

Number of sit-to-stands
Duration (s)
Maximum acceleration (m/s^2)
Minimum acceleration (m/s^2)
Peak total sagittal lower extremity support moment (%Bodyweight*Height)
Peak sagittal trunk angle (deg)
Peak medial quadriceps-medial hamstrings co-contraction
Peak knee adduction moment (%BodyWeight x Height)
Peak knee flexion moment (%BodyWeight x Height)
Peak knee flexion (deg)
Balance Measures
Center of pressure displacement in A-P direction (mm)
Center of pressure displacement in M-L direction (mm)
Mean center of pressure velocity (mm/s)

Strength Assessment

Participants' strength will be evaluated with an isokinetic dynamometer through tasks of knee flexion and extension on the side of the index joint. Tests include maximal isometric extension torque (x3), maximal isometric flexion torque (x3), isokinetic flexion-extension at 60 deg/s (x2), and isokinetic flexion-extension at 120 deg/s (x2). Additionally, isometric plantarflexion trials (x2) will be recorded for the purpose of EMG normalization.

Device to be used: Biodex System 3

Raw Data obtained:

- Torque
- Angular position
- Angular velocity

Derived measures:

- Isometric testing
  - Peak extensor torque (Nm/kg)
  - Peak flexor torque (Nm/kg)
- Isokinetic testing
  - Peak extensor torque at 60 deg/s(Nm/kg)
  - Peak flexor torque at 60 deg/s (Nm/kg)
  - Peak extensor torque at 120 deg/s (Nm/kg)
  - Peak flexor torque at 120 deg/s (Nm/kg)

In-lab Functional Assessments (only wrist and lumbar sensors will be worn during these tests)*:*

- *Stair climbing test (SCT)*
  - Ascending and descending a flight of stairs (x2)
  - Will only be assessed during in-lab visits

- *6-minute walk test (6MWT)*
    - Distance covered in 6 minutes
    - Will only be assessed during in-lab visits
- *15-second step-up test:*
    - Number of step-ups in 15-second (4in step)
    - Will be assessed during both in-lab and at-home visits
- *7-meter gait test*
    - Get up from a chair, walk 7 meters, turn around, return to starting position, sit down
    - Will be assessed during both in-lab and at-home visits
- *Short Physical Performance Battery (SPPB)*. SPPB includes the following tests
    - Balance tests (all performed with eyes open and under close supervision of a study staff member)
        - Side-by-side stand – standing with feet side-by-side for 10 seconds
        - Semi-tandem stand – standing with side of the heel of 1 foot touching the big toe of the other foot for 10 seconds
        - Tandem stand – standing with the heel of one foot in front of and touching the toes of the other foot for 10 seconds
        - Will only be assessed during in-lab visits
    - Gait speed text (x2)
        - walking over a 4-meter walkway
        - Will only be assessed during in-lab visits
    - Single chair stand
        - Will only be assessed during in-lab visits
    - Repeated chair stands i.e., 5 chair stands (x2)
        - Will only be assessed during both in-lab and at-home visits

Functional Assessment	**Clinical Metric**	**Lumbar Sensor Measures**	**3-sensor inertial system**
Stair Climb Test	Time to complete (sec)	NA	NA
15-second step-up test	Number of step-ups	NA	NA
6-minute walk test	Total distance traveled (meters)	Metrics will be calculated with in-house algorithms	Same metrics as lumbar sensor
7-meter gait test	NA	Metrics will be calculated with in-house algorithms	Same metrics as lumbar sensor
SPPB	Total balance test score Gait speed test score Chair stand test score Total score	Metrics will be calculated with in-house algorithms	Same metrics as lumbar sensor

6.1.2 In-Lab Pain Phenotype Assessments:

<u>Quantitative Sensory Testing (QST) and Exercise-Induced Hypoalgesia (EIH)</u>

Devices to be used: Medoc AS00301 AlgoMed Computerized Algometry System; von Frey monofilament set, Blood pressure cuff.

The QST is a valuable method for evaluating pain sensitization by examining the nociceptive response after application of different painful stimuli of controlled intensity to assess the function of both large and small nerve fibers and its central pathways.

Raw Data obtained:

- Pressure pain threshold (PPT): at the index knee joint and a wrist joint (in kgf)

Tasks to be performed:

- **PPT:** refers to the pressure at which the person first notes the pressure changing to slight pain. The pressure is applied using a hand-held algometer at the index knee and an uninvolved wrist (control site). PPT assessed at a site of disease (e.g., knee with OA) is a reflection of peripheral +/- central sensitization, whereas when it is assessed at an otherwise undiseased site (e.g., wrist as the referent site), it is a reflection of central sensitization. Three trials are performed at each site and the average of the last two trials is used in the analysis. Lower scores indicate greater "pressure pain sensitivity". The outcome is the mean PPT (in kgf) across the three trials.
- **Temporal Summation (TS):** refers to the increased perception of pain from repetitive stimuli applied at a uniform interval. An exaggerated TS of pain characterizes many chronic pain conditions and is related to central sensitization. TS will be assessed by repeated pressure stimuli using a series of weighted monofilaments until a weight that evokes pain ≥ 4/10 is reached. This weighted monofilament will then be applied 10 times at a rate of 1Hz. The participant's response will be assessed immediately after the train of 10 stimuli, as well ass 15 seconds and 30 seconds after completion on a numeric pain rating scale (from 0 to 10). TS will be considered to be facilitated if a positive value is obtained after the initial pain rating is subtracted from the greatest of the 3 post-stimuli pain ratings.
- **Conditioned Pain Modulation (CPM):** This test assesses the descending modulatory pathways, wherein the pain experienced by one noxious stimulus is diminished when a second conditioning noxious stimulus is appied. CPM will be assessed using the forearm ischemia test. The first PPT is obtained as described above. Then a blood pressure cuff is applied to the contralateral arm and inflated to above systolic. The participant then performs hand grips with a squeeze ball until the s/he rates their forearm pain as ≥4/10, at which point a second PPT is obtained; if this is not achieved within 2 minutes, the second PPT is obtained. A ratio of the second PPT to the first PPT is an indication of CPM. A ratio that is =<1, indicating lack of increase in post-conditioning stimulus PPT will be defined as impaired CPM and a ratio >1 will be noted as normal CPM.
- **Exercise-Induced Hypoalgesia (EIH):** is a form of endogenous pain modulation and corresponds to the attenuation of pain following a single episode of exercise. EIH will be assessed as the change in PPT at the study knee before and after a quadriceps and hamstrings strength testing protocol. A reduction in PPT is considered a positive EIH.

Derived measures:

  - PPT (kgf)
  - Temporal summation (yes/no)
  - CPM (yes/no)
  - EIH (yes/no)

6.1.3 Real World (at-home) Wearable Devices Assessments

Wearable devices capture and records high resolution raw acceleration data, which is converted into a variety of objective activity and sleep measures using both proprietary and publicly available algorithms. Data obtained will be used to evaluate performance (Gait and Sit-to-stand) and activity level (Steps and Activity Bouts; Intensity, and Energy Expenditure; Body Position; Sleep Onset)

Lumbar Sensor

The lumbar sensor will be applied at each in-lab visit and will be continued to be worn at home for a 7-day period following the in-lab visits (baseline, week 6, week 12 and week 18), , after which they will be mailed back. If the visit occurs at-home the participant will be mailed the sensor with instructions on application. The data will be processed using previously developed algorithms (e.g., GaitPy).

Proposed Device: Axivity AX6- 6-Axis Logging Accelerometer. Recording frequency: 100Hz.

Endpoints:

Gait measures
Cadence (steps/min)
Step length symmetry
Gait speed (m/s)
Stride duration (s)
Stride duration asymmetry (s)
Step duration (s)
Step duration asymmetry (s)
Initial double support time (s)
Terminal double support time (s)
Total double support time (s)
Single limb support time (s)
Stance time (s)
Swing time (s)
Step length (m)
Sit to stand measures
Number of sit-to-stands
Duration (s)
Maximum acceleration (m/s^2)
Minimum acceleration (m/s^2)
SPARC: SPectral ARC length

Wrist-worn sensor

The wrist sensor will be applied at the first in-lab (baseline) visit and continuously worn on the non-dominant wrist throughout the entire duration of the study. If the visit occurs at-home the participant will be mailed the wrist sensor and given verbal and written instructions on how to wear the device.

Proposed Device: ActiGraph GTX9. Recording frequency: vendor's default.

Endpoints:

- Steps/day
- Time spent in moderate and vigorous physical activity (MVPA) (min)
- % wear-time in MVPA

- Sedentary time (min)
- % wear-time sedentary

6.1.4 Questionnaires

Baseline Only Questionnaires:

KOOS

KOOS is a widely utilized self-reported measures of lower extremity symptoms and function. It provides scores on symptoms, pain, activities of daily living, quality of life, and sports and recreation. The instrument will be administered as the 5-level Likert scale (0=none, 1=slight, 2=moderate, 3=very, 4=extremely). The KOOS in its entirety will be administered at baseline.

Mobile Device Proficiency Questionnaire (MDPQ)

The MDPQ was designed to assess the mobile device proficiency of older adults as technology proficiency has become increasingly important to perform activities of daily living (Roque et al, 2018). We will use the short version of the MDPQ which consists of 16 questions to assess participants' proficiency when using a mobile device with answers ranging from "1-Never tried" to "5-Very easily" resulting in a total score ranging from 16 to 90. We expect that higher scores of proficiency will translate into increased study compliance.

Multidimensional Outcome Expectations for Exercise Scale (MOEES)

The MOEES is a 15-item questionnaire that quantifies outcome expectations from following an exercise program (Wojcicki et al, 2009). For each item, participants indicate the degree to which they agree with each statement on a scale of 1 (*strongly disagree*) to 5 (*strongly agree*). The questions convey the overall expected effect of exercise on items such as strength, mood and overall health. Scores range from a minimum of 15 to 75. Higher scores are indicative of higher levels of outcome expectations for exercise and therefore hypothesized to be associated with higher physical exercise adherence and self-efficacy.

Center for Epidemiologic Studies Depression scale (CES-D)

The CES-D scale is a commonly used self-report measure of depressive symptoms (Radloff et al, 1977). It consists of 20 items each scored from 0 ("rarely") to 3 ("most or all of the time") with a total possible score of 60.

Modified Charlson Comorbidity Index

A modified version of the self-reported Charlson Comorbidity Index will be used that assesses the number and severity of various health conditions.

Repeated Questionnaires

KOOS-Remaining

KOOS is a widely utilized self-reported measures of lower extremity symptoms and function. It provides scores on symptoms, pain, activities of daily living, quality of life, and sports and recreation. The instrument will be administered as the 5-level Likert scale (0=none, 1=slight, 2=moderate, 3=very, 4=extremely). The KOOS in its entirety will be administered at baseline. The Sports/Recreation, Quality of Life, and Symptom subscale (except stiffness questions) will be administered at week 6, week 12, and week 18.

Treatment history

This includes x

Pain Survey:

This questionnaire includes the following sections. The pain survey will be administered at baseline, week 6, week 12, and week 18.

- 3-item pain catastrophizing scale: The Pain Catastrophizing Scale (PCS) is a 13-item self-report measure of catastrophizing in the context of actual or anticipated pain (Sullivan et al, 1995). The PCS measures catastrophizing in 3 facets: rumination, magnification and helplessness. It is a self-report measure and consists of 13 items, which are scored from 0 to 4 and result in a total possible score of 52. It has been studied in many acute and chronic pain cohorts and elevated scores have been found to correlate with pain severity and sensitivity, pain chronicity and disability. A short version consisting of 3 items will be utilized therefore with a total possible score of 12.
- Widespread Pain Index: A 4-question widespread pain index will be used to assess the severity of fatigue, trouble thinking or remembering, waking up tired, and other physical symptoms.
- Joint homunculus for number of painful joints: A body map will be used to identify all painful joints. A joint homunculus has been used to identify widespread pain and has been validated in numerous epidemiologic studies.
- Modified painDETECT©: The *painDETECT©* questionnaire is a patient-completed screening tool designed to detect neuropathic-like components in patients with chronic pain using a scoring system that ranges from 0 to 38. The PDQ has associated with neuropathic-like pain symptoms in different clinical scenarios, including osteoarthritis, lower back pain, fibromyalgia and malignancy (Freynhagen et al, 2006). Scores lower than 12 indicate a neuropathic-like component to be unlikely, whereas scores greater than 19 indicate a likely neuropathic-like component. A modified version that only includes questions 11-13 will be used.

Daily Questionnaires:

Daily Sleep Interference Scale (DSIS)

The Daily Sleep Interference Scale (DSIS) quantifies sleep interference due to pain and is an 11-point scale that asks the participant to "select the number that best describes how much your pain has interfered with your sleep during the past 24 hours" (Vernon et al, 2008). Response options range from 0 (Did not interfere with sleep) to 10 (Completely interfered with sleep/unable to sleep due to pain). Negative change from baseline scores indicate improvement (lessening) of how much pain interfered with sleep.

Medication log

This question will ask about whether the participant has taken any analgesic medications for joint pain or arthritis.

Exercise and activity log

This survey asks about the amount of physical activity (in minutes) performed by the participant and whether they completed their physical therapy home exercise program each day.

Weekly Questionnaires:

KOOS-Weekly

KOOS is a widely utilized self-reported measures of lower extremity symptoms and function. It provides scores on symptoms, pain, activities of daily living, quality of life, and sports and recreation. The instrument will be administered as the 5-level Likert scale (0=none, 1=slight, 2=moderate, 3=very, 4=extremely). The Pain and Function subscales, plus two questions on stiffness from the Symptom subscale will be administered each week.

Patient's Global Assessment of OA (PGA-OA)

PGA is commonly used for patient assessment of global health or of disease activity. In our study, participants will be asked to evaluate their impression of pain severity and global impact on daily activities by answering to the following question: *Considering all the ways your osteoarthritis in your knee affects you, how are you doing today?*; Participants will rate their condition using a 5-point Likert scale (1-very good, 2-good, 3-fair, 4-poor, 5-very poor).

Numeric Rating Scale for Pain with Nominated Activity (NRSna)

The NRSna is a single-item instrument that evaluates self-reported pain with the advantage of allowing individual variability as participants are asked to nominate an activity that most aggravates their pain and then providing a rating score within that context (Parkes et al, 2016). Participants will be asked to *"select an activity that is most troublesome due to your knee pain"* and will subsequently rate their knee pain over the past week during this activity using a numerc rating scale that ranges from 0 (zero – *no pain at all*) to 10 (*worst imaginable pain*).

Demographics

Demographical data including ethnicity, race, education, income, smoking history, employment status, insurance information, marital status, and weight history will be obtained at baseline assessment.

Week-18 Only Questionnaire:

Exit Survey

This questionnaire will include items on:

- Effect of PT: This will include questions on overall effect of PT, participant enjoyment with PT, and ratings of the intervention and interventionists. All questions will be asked using a 5-point Likert scale.
- Feedback on study: Participants will be asked to provide feedback on various aspects of the study including time commitment, in-lab testing, etc.
- Sensor comfort: Participant will be asked to provide feedback on their comfort with the sensors used in the study.

7. ANALYSIS PLAN

7.1. Analysis of Primary Aim and Endpoints

Details of the analysis of this study will be documented in the Statistical Analysis Plan (SAP). The analyses described in the approved SAP will be followed if different from what is described in this protocol.

Primary Aim: Measure the effect of PT on functional performance using digital measures from wearable sensors.

The following analyses will be performed to address this primary aim.

A. Validate wearable sensor-based metrics of functional biomechanical tests in people with knee OA against optical motion capture

Data from the lumbar sensor and optical motion capture during gait and sit-to-stand tasks during in-lab visits will be used for this analysis. Wearable sensor metrics will be compared against gold standard metrics from the optical motion capture system using intra-class correlation coefficient (ICC) and it's 95% lower and upper confidence limits. The ICC reflects both the degree of correlation and agreement between the measurements. We will interpret agreement between measurements according to the following benchmarks: ICC ≤ 0.4 indicates 'poor', 0.4 to 0.59 'moderate', 0.6 to 0.74 'good', and 0.75 to 1 'excellent' reliability (Cicchetti et al., 1994). In addition, we will also compute the mean, variance and percentage error between the standard and the digital measurements. Bland–Altman plots and 95% limits of agreement (average difference ± 1.96 standard deviation of the difference) will also be computed.

B. Compare wearable sensor-based metrics of physical performance in people with knee OA with standardized physical performance outcomes.

Wearable sensors with excellent reliability from analysis A will be examined. Sensor-based metrics from lumbar sensor during physical performance tests in-lab will be correlated with standardized physical performance outcomes using Pearson's product-moment correlations or Spearman's rank order correlations depending on their normality.

C. Assess the effects of exercise-based PT on outcomes from wearable sensors during in-lab physical performance tests

Wearable sensors with excellent reliability from analysis A will be examined. Mixed model repeated measures (MMRM) analysis will be used to investigate the effect of PT on endpoints derived from the lumbar sensor during in-lab physical performance tests. The outcome measures will be expressed as the change from baseline at each visit (i.e. 6 and 12 weeks). The model will include the baseline value of the outcome variable, week (as a categorical factor), and the interaction between the baseline value and week, as well as covariates such as age, sex, BMI, and presence of comorbidities. Unstructured covariance matrix will be assumed for the model errors. If visual inspection of the model diagnostics (i.e. residuals) suggest that a transformation of the endpoint should be performed, this will be applied as appropriate prior to analysis (i.e. change from baseline would be calculated on the transformed scale) and documented in the final report as required. The Least Squares Means (LSMeans) together with 95% confidence intervals will be obtained for each week and plots will be produced illustrating the trajectory of the LSMeans over time. The above outputs will be back-transformed to the original scale for transformed endpoints as required. Missing values will accounted for by utilizing a maximum likelihood-based approach as part of the MMRM assumptions.

The primary analyses will be applied to each endpoint separately. The Benjamini-Hochberg procedure will be used to control the false discovery rates (FDR). FDR will be set at 5% and adjusted p-values (i.e., q values) < 0.05 will be considered significant.

Sensitivity analyses will include (a) only in participants who attended at least 80% (14 visits) of the PT visits, and (b) in all participants stratified into < 6 PT visits attended, 6-12 PT visits attended, and >12 PT visits attended.

D. Assess the effects of exercise-based PT on outcomes from wearable sensors during at-home activities

Wearable sensors with excellent reliability from analysis A will be examined. The same MMRM approach and sensitivity analyses described above will be used to investigate change from baseline to 6- and 12-weeks with PT on at home endpoints. Mean/median across a valid period for each endpoint will be used in the analyses.

E. Assess the effects of exercise-based PT in-lab tests of physical performance.

The same MMRM approach and sensitivity analyses described above will be used to investigate change from baseline to 6- and 12-weeks with PT on physical performance outcomes.

F. Assess the effects of exercise-based PT using joint mechanics during in-lab functional biomechanical tests

The same MMRM approach and sensitivity analyses described above will be used to investigate change from baseline to 6- and 12-weeks with PT on endpoints derived from optical motion capture during in-lab visits.

Details of any sensitivity or supportive analyses, along with details of any multivariate analyses (i.e. including more than one endpoint in an analysis) will be fully documented and specified in the SAP.

7.2. Analysis of Secondary Aims and Endpoints

1. Compare in-lab and ambulatory (at-home) sensor metrics with ePRO outcomes

A. Compare change in in-lab wearable sensor metrics with ePRO outcomes

Wearable sensor metrics with excellent reliability from analysis A in Aim 1 and which show a significant change from baseline to 12-weeks during in-lab physical performance tests will be examined; ePRO measures from KOOS-derived WOMAC 3.0, KOOS, NRSna, PGA-OA that show a significant change from baseline to 12-weeks will be examined. Change from baseline to week 12 in sensor-based metrics from lumbar sensor during in-lab physical performance tests will be correlated with change in ePRO outcomes using Pearson's product-moment correlations or Spearman's rank order correlations depending on their normality.

B. Compare change in at-home wearable sensor metrics with ePRO outcomes

Wearable sensors metrics with excellent reliability from analysis A in Aim 1 and which show a significant change from baseline to 12-weeks during at-home wear will be examined; ePRO measures from KOOS-derived WOMAC 3.0, KOOS, NRSna, PGA-OA that show a significant change from baseline to 12-weeks will be examined. Change from baseline to week 12 in sensor-based metrics from lumbar sensor during at-home periods will be correlated with change in ePRO outcomes using Pearson's product-moment correlations or Spearman's rank order correlations depending on their normality.

2. Assess the effect of physical therapy on sleep using ePRO (DSIS questionnaire) and wearable sensor metrics

The same MMRM approach and sensitivity analyses described above will be used to investigate change from baseline to 6- and 12-weeks with PT on sleep outcomes.

3. Assess the persistence of the physical therapy effect from week 12 to week 18 using in-lab and ambulatory (at-home) sensor metrics, and ePROs

In-clinic and at-home endpoints that showed a significant change from baseline to week 12 will be examined. Similar MMRM approach to that described above will be used to investigate change in outcomes from baseline to 18-week

timepoints. The outcome measures will be expressed as the change from baseline at each visit (i.e. 6, 12 and 18 weeks). We compare the effects at week 12 and week 18 by using linear contrasts.

7.3. Analysis of Exploratory Aims and Endpoints

1. **Assess whether sensor-based baseline measures can stratify treatment response**

Wearable sensors with excellent reliability from analysis A in Aim 1 will be examined. Sensor data lumbar sensor during in-lab physical performance testing will be modeled as continuous exposure, as well as, tertiles. Multivariate logistic regression will be used to assess whether baseline wearable sensor metrics can predict treatment response while accounting for confounders such as age, sex, BMI, and baseline KOOS-derived WOMAC 3.0 pain score.

2. **Assess whether participant phenotype; pain, physical performance, affective traits (catastrophizing), can stratify treatment response.**

The following exposure definitions will be used.

- Pain phenotypes
    - Tertiles of PPT
    - Presence/absence of TS
    - Inadequate/adequate CPM
    - Inadequate/adequate EIH
    - Presence/absence of pain catastrophizing from pain catastrophizing questions
    - Presence/absence of widespread pain from joint homunculus
    - PainDETECT score (continuous)
- Physical performance
    - Tertiles of physical performance tests
    - Tertiles of strength tests

Multivariate logistic regression will be used to assess whether baseline exposure vairables can predict treatment response while accounting for confounders such as age, sex, BMI, and baseline KOOS-derived WOMAC 3.0 pain score.

7.4. Analysis of Substudy Data

To address the aims of the substudy, gait and activity metrics will be derived from sensor data collected at home and in-lab using vendor-provided and in-house algorithms.

1. **Examine the test-retest reliability of at-home instrumented physical performance tests**

Test retest reliability of physical performance tests (7-meter gait, 5 times sit to stand) will be assessed using ICC and correlation analyses on sensor metrics (from 3-sensor IMU system and lumbar sensor) derived from data collected during the two sets of at-home tests.

2. **Examine agreement between wearable sensor data collected during in-lab and at-home instrumented physical performance tests**

Agreement between wearable sensor data (from 3-sensor IMU system and lumbar sensor) collected during in-lab and at-home physical performance tests (7-meter gait, 5 times sit to stand) will be assessed using ICC analyses as well as Bland–Altman plots and 95% limits of agreement on the derived sensor metrics.

8. RECRUITMENT

Recruitment strategies include but are not limited to:

- Data-driven recruitment via social media using services of TrialFacts (https://trialfacts.com/).
- Flyers placed around Boston Medical Center and Boston University neighborhoods
- Advertisements in local print media (senior center newsletters, church newsletters, local newspapers) and online platforms (e.g., Craigslist)
- Flyers places in the waiting rooms for local primary care practices
- Seminars and recruitment sessions at senior centers, churches, and other sites where older adults gather
- Boston Medical Center Clinical Data Warehouse

9. CONSENT

The documents used during the informed consent process and any participant recruitment materials will be reviewed and approved by the study site institutional review board. The informed consent documents and any participant recruitment materials will be in compliance with local regulatory requirements and legal requirements, including applicable privacy laws. The investigator will ensure that each study participant is fully informed about the nature and objectives of the study, the sharing of data relating to the study and possible risks associated with participation, including the risks associated with the processing of the participant's personal data. The investigator further will ensure that each study participant is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

The investigator, or a person designated by the investigator, will obtain written informed consent in-person from each participant before any study-specific activity is performed. The investigator will retain the original of each participant's signed consent document. The informed consent document will specify that the investigators will not attempt to connect any data back to any individual. During the study, if participants sustain an injury they will be instructed to immediately contact the study PIs (Tuhina Neogi or Deepak Kumar). There will be no program in place to provide compensation for the cost of care for research related injury or other expenses (such as lost wages, disability, pain or discomfort). The participant and/or their insurance will be billed for the medical care they receive for a research injury.

Participants may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral, or administrative reasons. In any circumstance, every effort should be made to document participant's outcome, if possible. The investigator should document the reason for withdrawal and follow-up with the participant regarding any unresolved adverse events.

If the participant withdraws from the study, and withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The study team may retain and continue to use any data collected before such withdrawal of consent.

10. PARTICIPANT COMPENSATION

Participants will be compensated for participation in study based on lab visits. Table 2 indicates the compensation schedule for participant participation. Participants will not be separately compensated for physical therapy treatment.

Participants in the substudy who complete the additional baseline at-home visit will be provided $25.

Participants in the substudy who are randomized to undergo the at-home visit prior to in-lab visit, an additional visit for consenting and providing the tablet computer will be needed. Participants will be paid $25 for completing this visit.

All participants will be provided with a tablet computer to complete remote tasks and will be allowed to keep the tablet after the study is complete.

Participants will be provided $15 for the in-clinic PT visits to cover parking costs (if cab fare is not provided).

Table 2: Participant Compensation

Visit	Time (hours)	Amount (per participant)	Estimated # of Participants
Consent Visit (for those randomized to complete at-home visit prior to in-lab visit in substudy)	1	$25	5-10
Sub-study At-home Visit	1.5	$25	11-20
Baseline	4	$50	60
Week 6	3	$60	60
Week 12	4	$100	60
Week 18	4	$125	60
End of Study (return of devices)	0.5	$100	60
Total Compensation (all visits and device return complete)	16	$485	60

11. CONFIDENTIALITY OF DATA AND PRIVACY OF PARTICIPANTS

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of research participant personal data. Such measures will include omitting names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

All personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff has access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law. Records may be disclosed when required for audit or review of the research conducted by federal or states agencies (such as the US Department of Health and Human Services, the Food and Drug Administration, the National Institutes of Health, and the Massachusetts Department of Public Health). Additionally, data may be shared with Pfizer or Boston University subcontractors analyzing the data.

To protect the rights and freedoms of natural persons about the processing of personal data, when study data are compiled for transfer, participant names will be removed and will be replaced by a single, specific, numerical code, based on a pre-defined numbering system defined by the study site. The investigator site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to their actual identity.

12. MONITORING OF STUDY DATA

The clinical tests used in this study offer minimal risks to participants and will be administered by an experienced team in working with this patient population. Participants will be asked to report all activity-related symptoms of pain or discomfort to the investigator, who will decide if medical care is warranted, and arrange for that care as appropriate. Participants will be constantly supervised and assisted as necessary throughout their testing and training session.

Approval of protocol, informed consent procedures, and recruitment will be obtained from the study site IRB during annual reviews. Because this study's procedures pose relatively low risk to participants, monthly data and procedural reviews by the PI in consultation with study staff will be sufficient to identify and ameliorate any potential safety issues. Any safety concerns about the exercise or clinical protocol will be brought to the immediate attention of the PI.

13. REFERENCES

Bolink SA, van Laarhoven SN, Lipperts M, Heyligers IC, Grimm B. Inertial sensor motion analysis of gait, sit-stand transfers and step-up transfers: differentiating knee patients from healthy controls. Physiol Meas 2012;33(11):1947-58.

Cicchetti DV. Guidelines, criteria, and rules of thumb for evaluating normed and standardized assessment instruments in psychology. Psychological Assessment 1994;6(4), 284–90.

Ferreira GE, Robinson CC, Wiebusch M, Viero CC, da Rosa LH, Silva MF. The effect of exercise therapy on knee adduction moment in individuals with knee osteoarthritis: A systematic review. Clin Biomech 2015;30(6):521-7.

Fransen M, McConnell S, Harmer AR, van der Esch M, Simic M, Bennell KL. Exercise for osteoarthritis of the knee: a Cochrane systematic review. Br J Sports Med 2015;49(24):1554-7.

Freynhagen R, Baron R, Gockel U, Tölle TR. painDETECT: a new screening questionnaire to identify neuropathic components in patients with back pain. Curr Med Res Opin 2006; 22(10):1911-20.

Goh SL, Persson MSM, Stocks J, Hou Y, Lin J, Hall MC, Doherty M, Zhang W. Efficacy and potential determinants of exercise therapy in knee and hip osteoarthritis: A systematic review and meta-analysis. Ann Phys Rehabil Med 2019;62(5):356-65.

Lim BW, Hinman RS, Wrigley TV, Sharma L, Bennell KL. Does knee malalignment mediate the effects of quadriceps strengthening on knee adduction moment, pain, and function in medial knee osteoarthritis? A randomized controlled trial. Arthritis Rheum 2008;59(7):943-51.

Page CJ, Hinman RS, Bennell KL. Physiotherapy management of knee osteoarthritis. International Journal of Rheumatic Diseases 2011;14:145-151.

Parkes MJ, Callaghan MJ, O'neill TW, Forsythe LM, Lunt M, Felson DT. Sensitivity to Change of Patient-Preference Measures for Pain in Patients with Knee Osteoarthritis: Data From Two Trials. Arthritis Care & Research 2016;68(9):1224-31.

Radloff LS. The CES-D scale: A self-report depression scale for research in the general population. Appl Psychol Meas 1977;1:385-401.

Roque NA, Boot WR. A New Tool for Assessing Mobile Device Proficiency in Older Adults: The Mobile Device Proficiency Questionnaire. J Appl Gerontol 2018;37(2):131-156.

Sparkes V, Whatling GM, Biggs P, Khatib N, Al-Amri M, Williams D, Hemming R, Hagen M, Saleem I, Swaminathan R, Holt C. Comparison of gait, functional activities, and patient-reported outcome measures in patients with knee osteoarthritis

and healthy adults using 3D motion analysis and activity monitoring: an exploratory case-control analysis. Orthop Res Rev 2019;11:129–40.

Sullivan MJL, Bishop SR. The Pain Catastrophizing Scale: Development and Validation. Psychological Assessments 1995; 7(4): 524-32.

Vernon MK, Brandenburg NA, Alvir JM, Griesing T, Revicki DA. Reliability, validity, and responsiveness of the daily sleep interference scale among diabetic peripheral neuropathy and postherpetic neuralgia patients. J Pain Symptom Manage 2008;36(1):54-68.

Wójcicki TR, White SM, McAuley E. Assessing Outcome Expectations in Older Adults: The Multidimensional Outcome Expectations for Exercise Scale. J Gerontol B Psychol Sci Soc Sci 2009;64B(1):33–40.

Woolf A, Pfleger B. Burden of major musculoskeletal conditions. Bull World Health Organ 2003;81(9):646-56.

Czech et al., (2019). GaitPy: An Open-Source Python Package for Gait Analysis Using an Accelerometer on the Lower Back. Journal of Open Source Software, 4(43), 1778, https://doi.org/10.21105/joss.01778

Zou, G. Y. Sample size formulas for estimating intraclass correlation coefficients with precision and assurance. *Statistics in Medicine*. 2012.