



1-28-2021

Development of a Mind Body Program for Obese Knee Osteoarthritis Patients with Comorbid Depression

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Repository Citation

Jacobs, Cale A.; Mace, Ryan A.; Greenberg, Jonathan; Popok, Paula J.; Reichman, Mira; Lattermann, Christian; Burris, Jessica L.; Macklin, Eric A.; and Vranceanu, Ana-Maria, "Development of a Mind Body Program for Obese Knee Osteoarthritis Patients with Comorbid Depression" (2021). *Orthopaedic Surgery and Sports Medicine Faculty Publications*. 26.

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Digital Object Identifier (DOI)

<https://doi.org/10.1016/j.conctc.2021.100720>

Notes/Citation Information

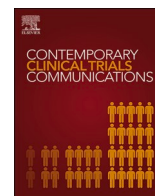
Published in *Contemporary Clinical Trials Communications*, v. 21, 100720.

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Development of a mind body program for obese knee osteoarthritis patients with comorbid depression

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ARTICLE INFO

Keywords:

Osteoarthritis
Depression
Obesity
Mind-body
Resiliency
Physical activity

ABSTRACT

Knee osteoarthritis (OA) is the most common joint disorder in the U.S. and a leading cause of disability. Depression and obesity are highly comorbid among knee OA patients, and the combination of obesity and depression is associated with decreased physical activity, higher pain and disability, and more rapid cartilage degradation. Depression, obesity and OA exacerbate one another and share a common pathophysiology involving systemic inflammation and pro-inflammatory cytokines, reflecting a complex mind-body interaction. Current treatments for knee OA offer little to no benefit over placebo, and do not emphasize mind-body practices or physical activity to target the underlying pathophysiology. Mind-body interventions to lessen depressive symptoms and increase physical activity offer the ability to target biological, mechanical and psychological mechanisms of OA progression. Our long-term goals are to evaluate the mechanisms by which the Relaxation Response Resiliency Program (3RP) delivered via secure telehealth, and adapted for patients with depression, obesity and knee OA (GetActive-OA) promotes increases in physical activity and improved knee health. We hypothesize that the synergistic interaction between mindfulness, adaptive thinking, positive psychology and healthy living skills of the GetActive-OA will slow the progression of symptomatic knee OA by reducing pro-inflammatory cytokine expression and promoting optimal mechanical loading of the cartilage. Here we present the protocol for a mixed methods study that will adapt the 3RP for the needs of knee OA patients with depression and obesity with a focus on increasing physical activity (GetActive-OA), and iteratively maximize the feasibility, credibility and acceptability of the programs and research procedures.

1. Introduction

Symptomatic knee osteoarthritis (OA) is the most common joint disorder in the United States and a leading cause of disability [1]. Depression and obesity are highly comorbid among knee OA patients [2, 3] and this combination is associated with decreased physical function [4,5], higher pain and disability, and more rapid cartilage degradation [6]. Depression, obesity and OA exacerbate one another and share a common pathophysiology [7–9] that involves a cycle of increased proinflammatory cytokine interleukin 1-beta (IL-1 β) and

Toll-like-receptor 4 (TLR4) [10–12] activity which, in turn, leads to inflammation-induced cartilage catabolism in the knee.

Current knee OA treatments offer little to no benefit over placebo, and do not emphasize mind-body practices linked with increased physical activity to target the underlying pathophysiology [13]. Increasing physical activity is particularly important as breaking the cycle of depression and inactivity associated with OA pain and cartilage degradation [5,14] can result in optimal loading of the articular cartilage. Light physical activities such as walking are associated with less knee pain [62] and may aid in preventing cartilage breakdown [63]. Walking is safe, commonly prescribed and preferred by patients.

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<https://doi.org/10.1016/j.conctc.2021.100720>

Received 27 May 2020; Received in revised form 29 September 2020; Accepted 11 January 2021

Available online 28 January 2021

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Abbreviations	
3RP	Relaxation Response Resiliency Program
ASES	Arthritis Self Efficacy Scale
BMI	Body mass index
CSQ	Client Satisfaction Questionnaire
CTX-I α	α isomerized version of the C-terminal crosslinked telopeptide of type I collagen
CTX-II	C-terminal crosslinked telopeptide type II collagen
ELISA	Enzyme-Linked Immunosorbent Assay
HEP	Health Enhancement Program
IL-1 β	Interleukin 1-beta
IMMPACT	Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials
IRB	Institutional Review Board
KOOS	Knee injury and Osteoarthritis Outcome Scale
MGH	Massachusetts General Hospital
MOCs	Measures of Current Status
MPGI	Modified Patient Global Impression of Change
MRI	Magnetic Resonance Imaging
NCCIH	National Center for Complementary and Integrative Health
NRS	Numerical Rating Scale
OA	Osteoarthritis
OARSI	Osteoarthritis Research Society International
OMERACT	Outcome Measures in Rheumatology
ORBIT	Obesity-Related Behavioral Intervention Trials
PCS	Pain Catastrophizing Scale
PHQ-9	Patient Health Questionnaire-9
RCT	Randomized Controlled Trial
RR	Relaxation Response
SMART	Specific, Measurable, Achievable, Relevant, and Time bound
TLR4	Toll-like-receptor 4
UK	University of Kentucky

However, sustained adherence is challenging due to multiple barriers including low mood, amotivation, weight, misconception about joint pain and stiffness, and inadequate problem solving and coping resources [15–20].

A mind-body intervention tailored to concomitantly address depression, obesity, and knee symptomatology integrated with quota based walking (e.g., gradual increase regardless of knee symptoms) has potential to increase knee function and slow OA progression through biological (e.g., reduced inflammation), mechanical (e.g., improved knee loading) and psychological (e.g., improved coping) mechanisms [21,22]. We previously adapted the Relaxation Response Resiliency Program (3RP) [17], a theory grounded, evidenced based mind-body program [18–23] for the unique needs of patients with chronic pain and to directly increase walking (GetActive program) [23,24] and showed high feasibility, acceptability, and satisfaction as well as a signal of improvement in pain, physical function, and emotional wellbeing. The GetActive program is amenable to further adaptations to directly address the interrelation of depression, obesity, knee dysfunction, as well as the older age of the typical knee OA patient, which present unique challenges to increased walking.

Here we describe the study protocol for Project DOORSTEP which entails three phases: 1) adaptation of the GetActive program for live video delivery and the unique needs of patients with knee OA (GetActive-OA) with depression and obesity through expert multidisciplinary feedback and live video focus groups; 2) exploration of initial feasibility, credibility and acceptability of GetActive-OA, live video delivery and

study procedures via an open pilot with exit interview; and 3) establishment of feasibility, credibility, acceptability and signal of improvement in all facets of physical function (accelerometer step count, 40 m Fast-Paced Walk Test, self-report) [23,25–28] and biomarker outcomes of the refined GetActive-OA versus the Health Enhancement Program (HEP) [29], an educational time and dose matched control via a pilot RCT. A live video program is necessary in order to reach this patient population who lives far from orthopedic centers and prefers this delivery modality. Results will inform a fully powered RCT of GetActive-OA versus the control to test efficacy and mechanisms of improvement through biological and psychological pathways.

2. Materials and methods

2.1. Mixed-methods design

Project DOORSTEP will use a mixed-methods approach to adapt, pilot and examine the credibility, acceptability, adherence and feasibility of GetActive-OA delivered via secure live video (Fig. 1). Our three-phase approach is consistent with Obesity-Related Behavioral Intervention Trials (ORBIT) [30] and National Center for Complementary and Integrative Health (NCCIH) models of intervention development, in which multiple program iterations are necessary to optimize feasibility and methodology before conducting larger efficacy clinical trials. Our team has applied these evidence-based frameworks and mixed-methods to adapt the 3RP for patients with heterogeneous chronic pain

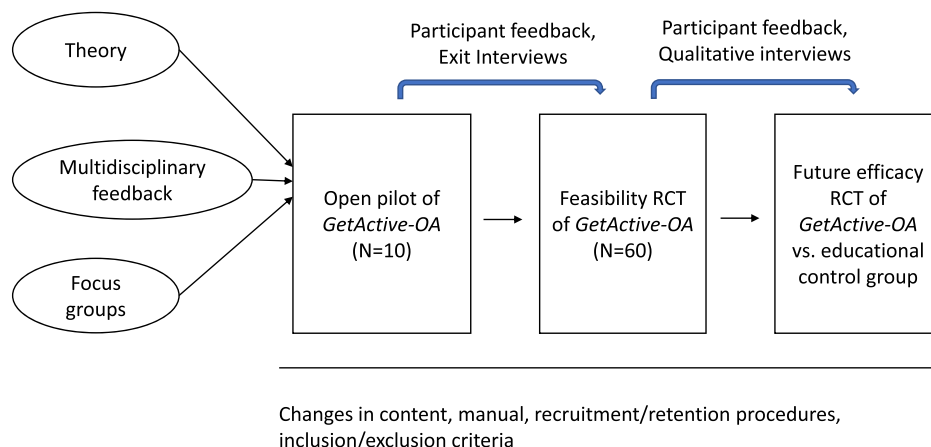


Fig. 1. Phases of Project DOORSTEP and development of the GetActive-OA program.

(GetActive program) [23,24] and neurofibromatosis and stroke [31,32]. The Institutional Review Boards (IRBs) at the University of Kentucky and Massachusetts General Hospital have approved all study procedures (IRB #53457). The research team and an external data safety and monitoring committee will provide ongoing oversight of project DOORSTEP.

2.2. Participants and recruitment

The same recruitment procedures and eligibility criteria will be used for all three phases of this project. Eight patients will be recruited to participate in the focus group interviews, eight patients will be enrolled in the open pilot study and complete exit interviews in Phase 2 (feasibility pilot), and 60 different patients will be enrolled in Phase 3 (feasibility RCT; up to 4 group cohorts of GetActive-OA each with 6–8 participants vs. up to 4 groups cohorts of HEP each with up to 8 participants). Eligible patients with mild to moderate knee OA, using standard diagnostic criteria, will be referred by seven physicians at the University of Kentucky (UK) Healthcare Hip & Knee Center and the UK Healthcare Orthopedic & Sports Medicine Center during regularly scheduled office visits. Standard diagnostic criteria will include clinical examination, patient-reported symptoms/functional limitations, and radiographic assessments. In addition, because the focus group activities can all be completed remotely, the IRB-approved study flyer will be circulated electronically at the participating institutions.

Inclusion criteria are: obesity (BMI ≥ 30 kg/m²), idiopathic knee OA [33] with mild to moderate radiographic changes (Kellgren/Lawrence grade 2 or 3³⁴ or Knee injury and Osteoarthritis Outcome Scores (KOOS) consistent with knee OA [35]), elevated depressive symptoms (PHQ-9 ≥ 10 ³⁵[36,37]), age 45 or older [38,39], history of concurrent psychotropics for < 2 weeks prior to initiation of treatment or on stable doses for > 6 weeks, access to an internet-enabled computer/smart phone, willingness to comply with the study protocol and assessments, and cleared by a medical doctor to participate. Exclusion criteria are: any disorder requiring the use of systemic corticosteroids; rheumatoid arthritis; history of cancer within 5 years of screening; unable to walk/wheelchair-bound; prior surgical fixation of a femur or tibia fracture; taking high doses of opioid pain medication (>50 mg of morphine equivalent per day); diagnosis of a medical illness expected to worsen in the next 6 months (e.g., malignancy); active suicidal ideation or past-year psychiatric hospitalization; non-English speaking; lifetime history of schizophrenia, bipolar disorder, or other psychotic disorder; current substance abuse or dependence (or a history within the past 6 months); practice of yoga/meditation, or other mind body techniques once per week > 45 min within the last 3 months; engagement in regular moderate or vigorous physical exercise for >30 min daily. These criteria are consistent with other clinical trials in knee OA or mind-body interventions [31,39]. Patients with reduced or altered capacity due to administration of any mind-altering substances such as tranquilizers, conscious sedation or anesthesia, brain injury, or age outside of the targeted range will not be recruited for participation in this study.

Enrollment and baseline data collection (self-report questionnaires, blood draws, urine samples) will coincide with the patient's office visit with their treating physician and will not require an additional visit. After providing verbal consent, potential participants will meet with a research assistant for study screening. If the screening indicates that the patient meets all inclusion and exclusion criteria, study staff will begin the written informed consent process.

Eligible participants will undergo written informed consent prior to the focus group interview (Phase 1) or baseline assessments (Phases 2–3). Due to the sensitive data collected in this study, patients will review and sign the combined informed consent and HIPAA-authorization if they choose to participate. The informed consent process will take place in a dedicated research room at either facility to ensure that both the patient and research team have adequate time and privacy. A specific item will be included on the Informed Consent and Data Collection

Checklist Forms to ensure that "Patients were asked if they had any questions (Yes/No)." The patient will then be given the option to provide informed consent that day, to return on a different day, or opt out. Study staff will coordinate scheduling to continue the informed consent process with patients as needed. A copy of the completed informed consent will be given to patients, added to their medical records, and documented in study progress notes.

2.3. Live video delivery

Participants will be recruited in-person at the University of Kentucky, but will also be recruited via electronic means at the other study sites (Massachusetts General Hospital (MGH) and Brigham & Women's Hospital (BWH)). The focus groups and intervention will be performed remotely by the study team at MGH. All three phases will be conducted via live video through a HIPAA-approved software used in clinical practice at MGH for a variety of medical populations. We have extensive experience with delivery of similar mind-body programs and focus groups via live video.^{102,121} We plan to start with this prior methodology and modify it as needed based on information from the focus group. After enrollment, participants will receive an emailed link for one-click installation of the video software. A research assistant will offer participants a test call and assist with installation as needed. Participants will receive a reminder email about the appointment information and a link to access the virtual group session. The research assistant will be available to assist participants in real time with any technical challenges they may experience during the focus groups (Phase 1) and treatment sessions (Phases 2 and 3).

2.4. Phase 1: development of the GetActive-OA program

The goal for Phase 1 of project DOORSTEP is to develop the GetActive-OA program. First, we will use existing literature and multidisciplinary expertise to propose modifications to the original GetActive program. Next, we will develop a semi-structured qualitative interview guide to conduct live video focus groups to gather feedback from the target population on the GetActive-OA and Project DOORSTEP procedures. All proposed changes will be finalized after these interviews, and other revisions will likely occur after the open pilot and exit interviews.

2.4.1. Conceptual model for GetActive-OA

Fig. 2 presents the conceptual model of GetActive-OA that will guide adaptations for the GetActive program. We hypothesize that participation in the GetActive-OA will be associated with decreased pro-inflammatory IL-1 β and TLR4 expression, increased resiliency skills (e.g., increased mindfulness and OA self-efficacy, and decreased pain catastrophizing) and increased physical function (measured through self-report, walk test, and accelerometer). In turn, these factors will be associated with decreased depression and obesity, leading to better knee health (i.e., decreased cartilage biomarkers, decreased pain/stiffness, and increased function). The GetActive-OA will thus directly target the 3 causal pathways associated with rapid knee degradation: biological, mechanical and psychological. Although not depicted in this figure, several relationships are bidirectional, including those between inflammation and depression, inflammation and obesity, and physical function and depression [40–44].

2.4.2. Program structure and modification

The GetActive-OA program will retain core components of the GetActive program, including (1) mind-body skills to elicit relaxation (e.g. deep breathing, mindfulness meditation); and minimize negative reactivity to pain and reduce activity avoidance; (2) cognitive behavioral skills that are pain-specific (e.g., behavioral activation techniques, goal-setting, adaptive restructuring of negative reactions to pain such as catastrophizing and fear avoidance) to remove barriers to getting active,

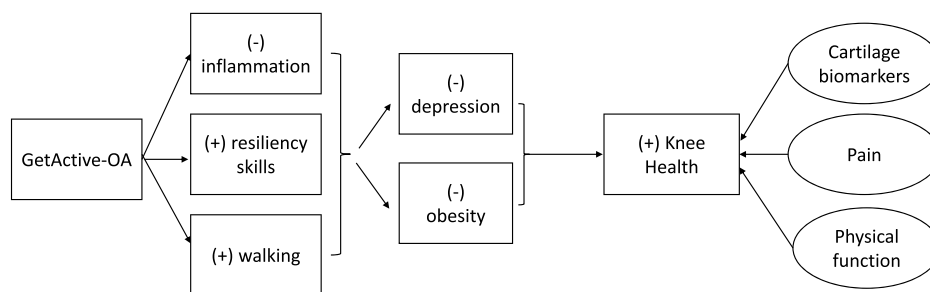


Fig. 2. Conceptual model of GetActive-OA for obese knee osteoarthritis patients with comorbid depression targeting the 3 pathways of rapid knee degradation (biological, mechanical and psychological).

and (3) skills for physical restoration (e.g., quota-based pacing non-contingent on pain) to systematically increase walking. We will adapt these skills to meet the specific needs, preferences, and challenges of patients with knee OA and comorbid depression and obesity (Table 1).

We will also add several novel components to the GetActive-OA

Table 1
Proposed modifications of GetActive-OA.

Session	GetActive Skills	GetActive-OA Proposed Modifications
1	Pain myths, body awareness, pain disability spiral, setting activity SMART goals, quota-based activity pacing, gratitude	Myths about knee OA; disability spiral of knee OA, obesity and depression; setting activity SMART goals; quota-based activity pacing; gratitude
2	Activity barriers, pairing steps with activities of daily living, relaxation vs. stress response, deep breathing, single-pointed meditation, body scan, sleep hygiene	Self-compassion with body image; depression and setbacks with goals; walking barriers; relationship between mood, pain, and activity; pairing walking with activities of daily living; deep breathing; single-pointed meditation; body scan; sleep hygiene
3	Mindful awareness, mindfulness of pain, stress warning signals, social support, the pain cycle, walking meditation	Mindfulness for knee OA, depression, and hunger cues; mindfulness of knee pain or discomfort; social support and coping with the stigma of pain, depression and obesity; effective communication; walking meditation
4	Movement to illicit the relaxation response, pairing activity with mind-body skills, negative automatic thoughts and adaptive thinking	Yoga for knee health; mindfulness of pain and discomfort; mindful walking; noticing the benefits of walking; negative automatic thoughts and common “thinking traps” in knee OA, depression and obesity; adaptive thinking; acceptance-based skills
5	Guided imagery, adaptive thinking, healthy eating, “Stop, Breathe, Reflect, Choose” for stress and pain	Healthy active self (guided imagery on visualizing a happy active life and a healthy knee); Mindful eating; “Stop, Breathe, Reflect, Choose” adapted for eating choices, coping with pain and depression
6	Loving kindness meditation, cultivating optimism, relaxation signals, “Getting Back on Track” after a lapse in activity	Loving kindness meditation (emphasis on depression and obesity-related self-criticism), cultivating optimism, “Getting Back on Track” after a lapse in activity
7	Problem solving and acceptance, empathy and compassion, contemplation-based meditation for pain management and activity	Acceptance versus change dialectic in pain and OA, meditation on acceptance versus change
8	Humor and laughter, “Idealized Self” for continued skills use after the program, staying resilient for pain management, overview of resiliency skills	Humor and laughter, “Idealized Self” for continued skills use after the program, staying resilient for pain management, overview of resiliency skills

program. First, we will provide educational information on the biopsychosocial interactions among knee OA, depression, and obesity that comprise a population-specific disability spiral. Inflammation is the biological tie among the 3 conditions and physical activity is a modifiable factor that can decrease inflammation, improve the biology and function of the knee, and decrease both depression and obesity [7–9, 45–52]. This will be used to provide a rationale for learning skills to directly address the 3 comorbidities, all of which are known barriers to increasing physical function and walking.

Second, we will directly address obesity by making novel modifications to the healthy eating educational information in the original 3RP. Participants will be taught to apply mindfulness skills to eating (mindful eating, noticing automatic urges) using behavioral economics principles (e.g., food shopping and placement), and engaging the entire family structure to make changes in diet and exercise.

Third, we will strive to reduce stigma faced by patients with these comorbidities. Our multidisciplinary team will revise the treatment manual for patient-sensitive language. Patients will learn to practice self-compassion to reduce self-criticism common in patients with depression and obesity, to prevent discouragement and dialectics (e.g., acceptance versus change) and to address ambivalence with making lifestyle changes.

Fourth, when discussing and targeting coping with the physical sensations associated with knee OA, rather than focusing exclusively on pain, we will specifically address other types of physical discomfort common in patients with knee OA, including stiffness, swelling, pressure, and limited range of movement. These post-activity sensations are often misinterpreted as damage and can further contribute to fear of pain, activity avoidance, and associated walking challenges that fuel the disability spiral [40–47]. We will reinforce that walking is safe [53], and associated with knee health.

Finally, although the 3RP, from which we developed the GetActive program, has been adapted for live video in patients with neurofibromatosis [31,32,54,55], we will optimize our live video procedures for this OA population. We are delivering the intervention to patients in rural areas who may have lower health literacy, which we have not done before. We will revise the manual with special attention to simplifying the language and eliminate less relevant skills from the GetActive program to reduce burden and allow more time for learning. We will consider developing specific practice aids (e.g., reminder calls or text, caregiver involvement). Patients with knee OA are able to successfully use technology (e.g., accelerometers, live video) if they perceive it as easy [56]. To this end, they will receive daily reminders to complete their home practice log on their smartphone [41].

We anticipate that the GetActive-OA will have eight 90-min sessions equally spaced over the course of 8 weeks; however, the exact structure will depend on the results of the focus groups. Participants will be assigned homework between sessions, which includes developing mindfulness and other meditation-based practices, writing down 3 appreciations, and setting a weekly SMART goal. SMART is an acronym to guide goal setting, standing for Specific, Measurable, Achievable,

Relevant, and Time bound.

2.4.3. Focus groups

We will identify the treatment needs and preferences of patients with comorbid knee OA, depression and obesity via 2 focus groups (N = up to 8 per group; 90 min). We will conduct the focus groups via live video to simulate participants in the intervention and elicit patient feedback on this delivery modality. The focus group interviews will be audio recorded and transcribed to further improve the GetActive-OA, tailor its live video delivery, and inform data collection procedures including blood and urine biomarkers. We will develop a semi-structured qualitative interview guide to gather feedback on: (1) challenges of living with comorbid knee OA, depression, and obesity; (2) patients' experiences with medical and complementary treatments; (3) knowledge about exercise recommendations for knee OA and interest in increasing walking; (4) perceptions of the GetActive-OA interventions; and (5) barriers to live video-delivery of the GetActive-OA, program adherence (group participation, homework completion), and data collection.

2.4.4. Phase 1 deliverables

After completing the focus group interviews, we will (1) refine the GetActive-OA manual to meet population-specific needs; (2) problem-solve potential barriers to adherence to in-session participation, homework and assessments (accelerometer, blood collection, self-reports); (3) solidify inclusionary and exclusionary criteria; and (4) finalize instruments to use in Phase 2.

2.5. Phase 2: open pilot and exit interviews

In Phase 2 of project DOORSTEP, we will conduct an open pilot of the newly developed GetActive-OA with individual exit interviews to explore preliminary credibility, acceptability, satisfaction with treatment, feasibility of recruitment, instruments, biological data collection, and adherence to homework and walking recommendations.

2.5.1. Open pilot

Procedure. The study clinician, a clinical psychologist with experience in mind-body interventions for heterogeneous pain conditions, will deliver one open pilot group (N = 8) of GetActive-OA via the secure video platform used for the focus groups. The first session of GetActive-OA orients participants to program expectations, which includes eight weekly live video group sessions (90 min each) and assigned home practice. Each week, the study clinician will introduce new GetActive-OA skills, guide participants in setting a walking SMART goal, assign home practice (walking, mind-body exercises, gratitude, and pain logs), and problem-solve adherence issues that emerge. Participants who achieved their walking goal from the previous week will be encouraged to increase their goal by 10–20% according to guidelines for quota-based pacing [57]. Participants who do not meet their step goal will be asked to reattempt (unsuccessful for one week) or lower (unsuccessful for two consecutive weeks) their step goal with the guidance of the study clinician. The research coordinators will troubleshoot technical difficulties with the live video platform and smartphone completion of the homework log. Participants that miss a group session will be contacted immediately by study staff and scheduled for a make-up of the GetActive-OA material.

The treatment fidelity process for the RCT will follow NIH recommendations¹²⁵ and our previously successful clinical adherence protocol [102]. The clinician will complete fidelity checklists after each session and will undergo weekly supervision to reinforce protocol adherence. All sessions will be audio-recorded, and a random sample (10%) will be coded by an independent coder to evaluate protocol fidelity for both the intervention and control. Depression severity and suicidality will be monitored within study procedures and reviewed weekly using our 3RP-specific live video risk assessment protocol [55]. Participants will be asked to provide information for 2 emergency contacts. All patients

will be informed that in the case of worsening of depression or suicidality by self-report, a warm hand-off will be done to connect the patient with a local clinical psychologist for a safety assessment. Participant referrals for appropriate levels of care will be completed as needed.

Assessments. The self-report measures and assessment domains were selected consistent with Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT), Osteoarthritis Research Society International (OARSI), and Outcome Measures in Rheumatology (OMERACT) recommendations [27,28], purpose of study [28], and recommendations for feasibility trials (Table 2) [30,58]. Before and after the GetActive-OA program, participants will be asked to travel to the local study site to receive their accelerometer and collect biological data.

Accelerometer data. ActiGraph wGT3X-BT accelerometers (ActiGraph, LLC, Fort Walton Beach, FL, USA) will objectively assess physical activity the week before and after the GetActive-OA intervention. This accelerometer is widely used to ecologically assess physical functioning outcomes in chronic pain and older adult trials [24,59–61]. Participants will be instructed to wear the accelerometer on a belt located at their natural waistline with the unit located on either their right or left hip in line with the axilla. Participants will be asked to wear the accelerometer from the time they awake until the time they retire (at least 10 h) except when in contact with water [60]. To optimize ActiGraph adherence, each participant will: (1) receive ActiGraph wear instructions (device placement, troubleshooting, when to remove it); (2) create an individualized wear plan with the study staff; (3) complete a daily standardized wear time log (time worn/off, physical activities); and (4) select preferred method of contact for daily reminders via phone, email, or texts. To reduce the observer effect, all participants will be instructed to maintain their current level of physical activity to the best of their ability. Participants will mail the accelerometers using prepaid envelopes after one week [62]. This procedure has led to high adherence in our prior research [23].

Biomarker data. Biomarkers analyses will utilize serum and urinary markers to avoid challenges associated with collection of knee synovial fluid [6]. The selected biomarkers have been shown to be predictive of inferior clinical outcomes and cartilage thinning [63,64], and are responsive to change over 3-month follow-up [65–67]. These validated biomarkers allow accurate assessment of short-term cartilage degradation and bone remodeling without the high cost or patient burden associated with imaging techniques such as magnetic resonance imaging (MRI).

CTXII and CTXI α will assess cartilage breakdown and bony remodeling, respectively. Following cartilage degradation, CTXII (C-terminal crosslinked telopeptide type II collagen) is released into the synovial fluid and the circulation. CTXII will be measured in the urine by ELISA (Cartilaps® (CTX-II); Immunodiagnostic Systems, Inc, Fountain Hills, AZ) [65,66], and will be normalized to creatinine levels (Quidel, San Diego, CA) [64,68]. CTXI α (an alpha isomerized version of the C-terminal crosslinked telopeptide of type I collagen) is localized to areas of high turnover of subchondral bone [68], and has been found to be predictive of OA symptom and radiographic progression [64]. CTXI α will be measured in the urine by sandwich ELISA (Nordic Biosciences, Herlev, Denmark), and like CTXII, will be normalized to urinary creatinine levels [64,68].

OA biomarker data collected will be carefully analyzed with respect to variability, linear range of standard, and need for repeat analyses. Controls provided with commercially available ELISA kits will be used with every run. For assays for which no control is available or provided, aliquots of serum from normal human subjects have been aliquoted and frozen at -80°C for this purpose. Each assay day, a fresh aliquot of this control serum is thawed and used on every plate to calculate intra- and inter-assay variance of the assay. In addition to the standard curve run in duplicate, this control will be run with each assay and the results used to determine the precision of the assay and to establish an acceptable control range for the assay. The mean of the control sample for all assays ± 2 standard deviations is defined as the acceptable control range. Any

Table 2
Assessments tools.

Construct	Measurement tool and schedule
Demographics	Age, biological sex, body mass index (BMI), race/ethnicity, educational level, employment status, occupation, income, marital status, mental health history, current psychotropic/pain medication intake, comorbid medical conditions, history of depression or other mental health conditions. Pre, Post.
Pain	<ul style="list-style-type: none"> Numerical Rating Scale (NRS) [69,70]; 11-point scale from 0 (no pain) to 10 (worst pain); Pre, Post. Use of rescue analgesics. Daily self-report log. Concomitant pain treatment. Daily self-report log. Pre, Post.
Physical Function: Self-reported	<ul style="list-style-type: none"> Knee injury and Osteoarthritis Outcome Score (KOOS) [71,72]; assesses OA pain, symptoms, and knee-related quality of life, and one's ability to carry out activities that require physical actions, ranging from self-care to social activities and work. Pre, Post.
Physical Activity: Objective and self-report	<ul style="list-style-type: none"> Accelerometer [73,74]; measure activity during 7 days both at baseline and post intervention. We will assess number of steps, as well as minutes of spent in light, moderate, and vigorous activity as well as minutes of sedentary time. Pre, Post. Physical Activity Scale for persons with physical disability (PASPD); assesses leisure, household and work activities. Pre, Post.
Physical Function: Performance-based	<ul style="list-style-type: none"> 40 m Self-Paced Walk Test [75,76]; assesses time necessary to walk 40 m. Pre, Post.
Emotional Function	<ul style="list-style-type: none"> PROMIS depression, v1.0.8b [77]; assesses negative mood, views of self and cognitions. Pre, Post. PROMIS anxiety, v1.0.8a [78]; assesses fear, worry, hyperarousal and somatic symptoms. Pre, Post.
Coping	<ul style="list-style-type: none"> Pain Catastrophizing Scale (PCS) [79]; assesses hopelessness, helplessness and rumination about pain. Pre, Post. Arthritis Self-Efficacy Scale (ASES); a valid 20-item instrument assessing self-efficacy in OA patients [80,81]. The ASES consists of 3 subscales (Pain, Function, and Other Symptoms) [80]. Pre, Post. Measures of Current Status (MOCS) [82]; assesses ability to engage in a series of healthy coping skills (e.g., relaxation, social support, adaptive thinking). Pre, Post.
Improvement (Patient's Perspective)	<ul style="list-style-type: none"> Modified Patient Global Impression of Change (MPGI) [83]; 2 item assessing the extent to which patients perceive the intervention improved functioning and symptoms. Post.
Credibility, Expectancy	<ul style="list-style-type: none"> The Credibility and Expectancy questionnaire (CEQ) [84] assesses treatment expectancy and credibility in clinical outcome studies. Pre.
Satisfaction	<ul style="list-style-type: none"> Client Satisfaction Questionnaire (CSQ-3) [85]; assesses satisfaction with program on 3 dimensions. Post.
Adherence to 3RP homework and activity	<ul style="list-style-type: none"> SMART goals; RR practice; Appreciations; Activity log. Adverse events. Daily self-report log.
Adherence to Accelerometer	<ul style="list-style-type: none"> Daily wear of Actigraph accelerometer for baseline and post intervention assessments. Pre, Post.
Cartilage breakdown	<ul style="list-style-type: none"> Urinary CTXII will be used to quantify cartilage degradation as this marker has been previously identified as being predictive of the progression of radiographic knee OA and knee OA symptoms [64, 68]. Pre, Post.
Bony remodeling	<ul style="list-style-type: none"> Urinary CTXII will be used to quantify OA-related bone turnover as this marker has been previously identified as being predictive of the progression of radiographic knee OA and knee OA symptoms [64]. Pre, Post.
Systemic inflammation	<ul style="list-style-type: none"> Proinflammatory cytokine IL-1β and Toll-like-receptor 4 (TLR4) will be assessed using ELISAs. Pre, Post.

samples on a plate in which the control falls outside of this range will be excluded and repeated. Samples will be run in duplicate and reanalyzed if the coefficient of variation is >15%. For values that are below the level of detection, a value equivalent to 0.5 lowest limit of detection will be recorded and used for statistical analyses [6,65,66].

2.5.2. Exit interviews

After the open pilot, we will audio record and transcribe in-person exit interviews conducted by the psychologist with each patient (30 min each). Exit interviews will assess: (1) the rationale and helpfulness of each GetActive-OA component for targeting knee OA, depression, and obesity; (2) perceived increase in physical function and usefulness of skills to increase walking; (3) experience with live video delivery (number and types of problems, satisfaction); (4) usefulness and adherence to home practice; and (5) burden and utility of assessments (biological samples, accelerometer compliance, self-reports) [23,32,86].

2.5.3. Phase 2 deliverables

After completing the open pilot, we will further refine the GetActive-OA intervention, manual and study protocol prior to initiating Phase 3's randomized controlled trial. We will also report markers of preliminary feasibility.

2.6. Phase 3: pilot randomized controlled trial

In Phase 3 of project DOORSTEP, we will conduct a pilot RCT of the GetActive-OA versus HEP. The goal of the pilot RCT is to assess the feasibility of recruitment procedures (e.g., screening, eligibility, enrollment rates), the feasibility and acceptability of the GetActive-OA and control interventions (e.g., adherence, retention, fidelity, satisfaction, group live video delivery), and the feasibility of data collection procedures by group (e.g., adherence, satisfaction, accelerometer data, blood and urine biomarker data). In line with common guidelines for feasibility studies [47], we will not test efficacy or perform between-group analyses.

We will enroll up to 60 patients and conduct up to 8 cohorts (4 GetActive-OA and 4 HEP control with 7–8 participants per group). Participants will be randomized in a 1:1 design using a randomization scheme developed by the study statistician. The procedures from Phase 2 will be repeated aside from strategies to optimize the protocol developed from the open pilot results.

The control group will have the same format and procedures as the GetActive-OA and will follow the format of the HEP [32]. We will modify this program for the specific needs of patients with knee OA. Session structure is outlined in Table 3. To control for between-session practice, participants will receive an audio recording and informational handout to complete after each session. All of the patient education information, in a simplified form, will be included in the GetActive-OA manual utilized by the research team. We have successfully used this procedure in our clinical trial in neurofibromatosis [32].

2.6.1. Phase 3 deliverables

We will calculate descriptive statistics for biochemical biomarkers of

Table 3
Structure of the Health Enhancement Program to be utilized with the control group.

Session	Health Enhancement Program Topics
1	Educational information on depression, obesity and knee function including the role of inflammation
2–3	Educational information on physical activity and effects on mood, weight and knee function
4–5	Educational information on nutrition
6	Educational information on sleep
7	Educational information on navigating medical care
8	Review

OA [6,66], depressive symptoms, body weight, physical function, and coping variables. We will also report definitive feasibility and acceptability markers for the GetActive-OA, the control intervention, and the study data collection and analysis procedures. This will provide a realistic assessment of the study procedures as they will occur during the fully-powered efficacy trial, information on how participants might engage differently with the intervention and control, and signal of improvement in the intervention before investment of resources in the full RCT.

2.7. Analysis plan

2.7.1. Qualitative data analyses (phases 1 and 2)

The focus group and exit interviews will be audio recorded, transcribed and iteratively analyzed using thematic content analyses following Miles and Huberman (1984) [87] in NVivo 11. The research assistant and clinician, who both have prior expertise in qualitative analyses, will conduct the analyses under the supervision of the research team's senior psychologist. Each transcript will be separately reviewed to identify common patterns and themes and develop a coding framework based on the interview scripts. Coding will be reviewed to ensure the reliability of the results. All discrepancies will be resolved through discussions with the research team's senior psychologist and by comparing codes to the raw data until a high level of reliability is reached ($Kappa > 80$) [23].

2.7.2. Quantitative data analyses (phases 2 and 3)

Blinded quantitative analyses and randomization will be overseen by the research team's statistician, who has extensive expertise in analyzing mind-body clinical trials across the stages of intervention development. We will report feasibility as number of participants approached, screened, eligible, and enrolled. We will report number of participants who completed at least 6 out of the 8 sessions (75%), along with the 95% confidence interval (CI) around this discontinuation rate. The research team's senior clinical health psychologist will assess adherence to treatment by listening to the audio recorded sessions and analyzing the therapist adherence checklists. The research team's senior psychologist will rate adherence for the 2 groups led by the study clinician in Phase 3. The research team's senior orthopedic researcher will assess the number of days participants wore the accelerometers at baseline and post-test using the active wear time of 10 h/day [60]. The research team's senior orthopedic researcher will assess the number of missing specimens as well as the number of samples with values below the limits of detection. We will also report information on preliminary acceptability from quantitative and qualitative data, as well as information on credibility of intervention and adherence to GetActive-OA home practice.

Consistent with guidelines for intervention development that emphasize a focus on feasibility prior to efficacy testing, feasibility markers were specified *a priori*. [21,29] Benchmarks provide clear guidelines for whether or not to move to an efficacy trial, or whether further modification of the intervention and study procedures are necessary prior to efficacy testing. The following benchmarks are required before undergoing the future fully powered RCT and have been used in our previous work: [23,34] 1) $> 70\%$ participants with Credibility and Expectancy score [84] and Client Satisfaction Scale Questionnaire (CSQ-3) [85], respectively, over each scale's mid-point; 2) more than 70% participants approached who agree to participate; 3) $> 70\%$ participate in at least 6 of 8 sessions; 4) more than 5 of 7 days of valid accelerometer data in $> 80\%$ of participants; 5) > 4 of 7 days relaxation response practice, SMART goal, appreciation, behavioral activation OR > 5 of 7 days for one of the 3 components by $> 70\%$ of participants; 6) $> 75\%$ therapist adherence to sessions (checklist and audio recordings); 7) no questionnaires missing fully in $> 25\%$ participants; 8) stable medications; 9) minimal adverse events (e.g., swelling, soreness, stiffness).

The main purpose of Phases 2 and 3 are to determine the feasibility,

acceptability, credibility and adherence of live video-delivered GetActive-OA. Neither trial is neither powered for efficacy nor aimed to provide such information. Consistent with the feasibility design of this trial, we will report means and standard deviations of all measures at all time points, including distribution of scores and internal consistency reliability. To determine the measures' sensitivity to detect change, we will report percent change in all quantitative outcomes within each group. We will also describe step count, types of activity (i.e., light, moderate and vigorous), and sedentary time measured by the accelerometers. Demographic and clinical variables will be summarized but efficacy analyses will not be conducted consistent with the R34 mechanism [88, 89]. In addition, biomarkers of cartilage degradation (CTXII), bony remodeling (CTXI α), and systemic inflammation (IL-1 β and TLR4) will be analyzed to determine if patient factors (e.g., age, biological sex, race, smoking status) influence biomarker concentrations to inform future analyses of covariate selection. Once these data analyses are completed, the multidisciplinary team will review the data and discuss the interpretation of our findings in the context of current research on OA-related pain and physical function.

3. Results

We have completed enrollment for the Phase 1 focus groups with enrollment estimated to begin in March 2021 for the Phase 2 open pilot and July 2021 for the pilot RCT. The target date of completing the pilot RCT is November 2022.

4. Discussion

Regular physical activity has been reported to slow the progression of OA and reduce pain and limitations [90], whereas sedentary lifestyles and reduced mechanical loading result in thinning of the cartilage [91–93]. Barriers to engaging and adhering to physical exercise in those with chronic pain include coping difficulties (e.g., low self-efficacy, fear avoidance, catastrophic thinking about pain), programs that are too challenging (e.g., going to the gym, doing too much too soon), not meaningful, interfere with one's life, or too difficult to implement [17–20]. Lack of physical activity and ineffective coping are common in individuals with obesity, depression and knee OA, and reinforce each other over time placing individuals on a disability spiral [45]. Depressed OA patients have a greater likelihood of reduced physical activity which may contribute to progressive cartilage degradation [5]. Depression, obesity, and knee OA are associated with sedentary behaviors and reduced physical activity [5], thereby creating a cycle of pain, inactivity, and cartilage degradation secondary to the systemic inflammatory burden for obese OA patients with depression. Walking is a safe physical activity in this population, preferred by participants, but challenging to adhere to and sustain over time.

Mind-body programs are effective in decreasing depression, obesity, and pain in a variety of populations [94,95], including OA [96,97], but there are several current limitations. First, mind-body programs do not directly target increased walking necessary for proper loading of the knee joint, which may represent one reason why complementary and alternative medicine approaches have not successfully slowed OA progression [98]. Walking also has direct effects on depression and weight and has the potential to increase the efficacy of the mind-body skills. Second, conceptualization and assessment of physical function in mind-body clinical trials do not follow guidelines for both pain-(IMMPACT) [27,28] and OA-related clinical trials (OMERACT-OARSI) [99,100] and do not incorporate self-report measures of activity of daily living (biased due to perceptions but important to patients), performance-based measures (e.g., walk tests; still subject to bias due to motivation and perceptions), and more objective measures of physical function such as accelerometers (which are valid and comparable to live observations of activity). Third, programs do not address the comorbidity of depression, obesity, and OA which are direct barriers to

increased walking in this population.

Our protocol was developed to directly address barriers to increased walking in this population, by adapting mind body skills to the unique needs of this population, and adding specific skills to help individuals set walking goals using quota based pacing. The proposed GetActive-OA will include SMART goal-setting in each session, evidenced-based skills previously found promising in chronic pain, OA, and depression when tested individually [101–104], embedded educational information on healthy lifestyle (walking, diet, sleep), and a focus on adjusting to symptoms, rather than eliminate them. These skills combined with increased walking can target biological, psychological, and mechanical OA pathways. Multimodal programs such as GetActive-OA, that incorporate a variety of skills are more efficacious than unimodal programs [105]. Multimodal mind body programs are successfully delivered via live video [31]. GetActive-OA patients may represent a viable treatment option for individuals with comorbid depression, obesity and knee OA at-risk patient population. The GetActive-OA will accommodate a 6th grade reading level allowing for patients with low health literacy or learning disabilities to participate.

The results of this mixed methods study will provide a realistic assessment of the study procedures as they will occur during the fully-powered efficacy trial, information on how participants might engage differently with the intervention and control, and signal of improvement in the intervention before investment of resources in the full RCT. These results will inform a fully powered RCT of GetActive-OA versus control to test efficacy and mechanisms of improvement through biological, psychological, and mechanical pathways. Our guiding hypotheses are that participation in the GetActive-OA will be associated with decreased pro-inflammatory IL-1 β and TLR4 expression, increased resiliency skills, and an improved ability to engage and sustain participation in regular walking. In turn, these factors will be associated with decreased pain, depression and obesity, leading to better knee health and quality of life.

4.1. Foreseen challenges

Despite the innovative approach of this project, there are potential challenges. Based on patients available at the involved orthopedic centers, recruitment goals should be attainable, but we will consider expanding effort for in-person recruitment to additional primary care and orthopedic centers in the region if needed. We have also adapted our recruitment and screening processes as a result of the COVID-19 response. Because the study procedures can be performed remotely without increasing risk to either the participant or research staff, the UK IRB has approved an study flyer that can electronically distributed at the participating institutions and circulated by patient advocacy groups such as the Arthritis Foundation. The informed consent process is completed with either electronic signatures or signed paper informed consent forms that can be either mailed or scanned and then emailed to the research staff. There may also be technological challenges for older knee OA patients when using live video. A research assistant will be available in real time to assist with any technological issues, consistent with our live video protocol for neurofibromatosis. If needed, we will offer accommodations for participants who need further assistance with the technology (e.g., set up on multiple devices, allowing participants to travel to a partnering clinic to participate in videoconferencing, offering webcams when not available, problem solving regarding travel to a family member's or friend's house to use other computers) as we have done in prior studies. Finally, patient retention could be potentially challenging. If group sizes fall below 3, we will consider adding incentives for adherence (e.g., giftcards for session adherence). We have not had this problem in any of our prior trials.

4.2. Implications

Approximately 1/3 of patients with knee OA experience a rapid progression of cartilage degradation, knee pain and disability [10]

leading to a greater utilization of healthcare resources [106]. [108] Patients with knee OA comorbid with both obesity and depression have significantly worse pain and subjective knee function, as well as significantly greater cartilage degradation than those without obesity or depression [6]. While it may seem that the subset of obese knee OA patients with comorbid depression is a very select subgroup, there is an impending “perfect storm” in terms of the prevalence of obese patients with comorbid depression that are predisposed to more rapid OA progression. The prevalence of obesity ranges between 37% and 40% for Americans above the age of 40 [109]. With the lifetime risk of developing symptomatic knee OA of 60% for obese individuals [110], it has been projected that more than 67 million Americans will suffer from OA by the year 2030 [111]. In addition, depression has been projected to be the most prevalent cause of disability by the year 2030 [112]. When one considers that approximately 20% of OA patients suffer from comorbid depression [113] and the increasing prevalence of obesity, knee OA, and depression, this seemingly narrow subset will soon include millions of Americans, making it a rising public health concern.

To address this growing public health concern, Project DOORSTEP aims to adapt the GetActive for the needs of knee OA patients with depression and obesity with a focus on increasing walking, and iteratively establish the feasibility, credibility and acceptability of the programs and research procedures. The goals of adapting the GetActive for this population are to both reduce depressive symptoms and optimize mechanical loading of the articular cartilage. In doing so, the GetActive-OA may reduce knee symptoms, improve function and slow cartilage breakdown. There is an opportunity to greatly improve quality of life in this population, and delivery of the GetActive-OA program via secure telehealth bypasses many barriers to care, including absence of skilled providers in remote areas, missed work, and/or burden of travel (cost and reliance on family and friends). This is particularly relevant in our area of Kentucky where many of our rural patients lack access to care, and telehealth is their self-reported preferred treatment modality.

By targeting modifiable influences of rapid OA progression and establishing a connection between comorbid obesity, depression, and the intraarticular knee environment, Project DOORSTEP will 1) provide for simple clinical methods to identify at-risk patients, and 2) trigger a line of innovative, multidisciplinary research to shift the treatment paradigm to move away from isolated treatment of the knee to a biopsychosocial model in which both the knee itself and the modifiable inflammatory conditions of obesity and depression are treated to potentially slow OA progression in the subset of patients at greatest risk.

Acknowledgements

This study is funded by a clinical trial grant awarded to CAJ and AMV by the National Center for Complementary and Integrative Health (NCCIH; R34 AT010370-01A1). The sponsor was not involved in the review or approval of this manuscript for publication.

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