MANUAL OF PROCEDURES

Telehealth exercise and mindfulness for pain in osteoarthritis (tempo) – A feasibility study

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1. List of Abbreviations

- OA: Osteoarthritis
- RCT: Randomized Controlled Trial
- PROMs: Patient Reported Outcome Measures
- TEMPO: Telehealth Exercise and Mindfulness for Pain in Osteoarthritis
- HIPAA: Health Insurance Portability and Accountability Act of 1996
- IRB: Institutional Review Board
- BV-R: Remote Baseline Visit
- BV-I: Optional In-person Baseline Visit
- RTT: Remote Randomization and Telehealth Training Visit
- W8-R: Remote Post-intervention Visit
- W8-I: Optional Post-intervention In-Person Visit
- W14: Remote Follow-up Visit
- BMI: Body Mass Index
- BP: Blood Pressure
- IMU: Inertial Measurement Unit
- 6MWT: 6-meter walk test
- SCT: Stair Climb test
- QST: Quantitative Sensory Testing
- PPT: Pressure Pain Threshold
- TS: Temporal Summation
- CPM: Conditioned Pain Modulation
- EIH: Exercise-Induced Hypoalgesia
- AE/SAE: Adverse Event/Serious Adverse Event
- fNIRS: functional near-infrared spectroscopy
- MMSE: Mini Mental State Examination
- PROMs: Patient Reported Outcome Measures

2. Study Design

2a. Study Abstract

Knee Osteoarthritis (**OA**) is a highly prevalent condition, [1-3] which poses a huge burden on the healthcare system. Exercise has been used as the first-line treatment for knee OA.[4,5] However, people with psychological factors such as high pain catastrophizing, low-self-efficacy, low mindfulness trait, fear of pain, and mood disturbances tend to have poor response to exercise treatments.[6-12] Additionally, neurobiological mechanisms such as central sensitization, characterized by hypersensitivity to pain stimulus due to abnormal neural signalling,[13] in people with chronic pain has been associated with poor response to exercise.[14] Mindfulness is a practice of non-judgment and moment-to-moment awareness.[15] There is an accumulating body of evidence that suggests that mindfulness can improve psychological factors such as pain catastrophizing, fear of movement, and pain hypersensitivity – factors that may be associated with poor response to exercise. Taking these evidence together, we posit that an intervention developed by combining mindfulness with traditional exercise treatments may increase the effectiveness of exercise alone. Before we test the effectiveness of such an intervention, we need to establish the intervention feasibility and acceptability.[16] *Therefore, the goal of this randomized controlled trial (RCT) is to determine the **feasibility** and **acceptability** of a mindful exercise program compared to exercise in people with knee OA.*

The Telehealth Exercise and Mindfulness for Pain in Osteoarthritis (TEMPO) is a longitudinal, parallel arm, 14-week clinical trial that will investigate the feasibility of an 8-week telehealth-delivered, group-based mindful exercise program. For this, forty people with knee OA will be recruited. These participants will be randomly assigned to either an 8-week mindful exercise program OR an 8-week exercise only program. Both programs will include weekly sessions (n=8 total) that will be delivered in a group setting (n=10 per group) by real-time videoconferencing (HIPAA-protected Zoom). Before the start of the interventions, all participants will attend an individualized remote randomization and telehealth training session where participant's group assignment will be randomized, and instructions for home set up and requirements for the remote sessions will be discussed. Participants will be administered surveys on pain, function, and mood before the start of the intervention (week 0), at post-intervention (week 8), and 6-weeks after the end of the interventions (week-14). Participants will be given an option to participate in two in-person visits at Boston University before the start (baseline visit) and at the end of the interventions (post-intervention visit). During these optional in-person visits, the participant's function, muscle strength, sensitivity to painful stimulus, and brain activity will be collected. Brain activity will be measured using functional near-infrared spectroscopy (fNIRS). At the end of the 8-week interventions, participants in the mindful exercise group will be invited to participate in individual interviews. The interviews will be conducted over Zoom to understand participant's perspective related to acceptability of the mindful exercise intervention

2b. Schedule of Visits

Figure 1 is a schematic diagram depicting the study flow. A list of measurements collected at each visit is shown below in **Table 1**. Apart from the research and intervention visits, the various timepoints of email and telephone contact with the participants in the study is shown in **Table 2**.

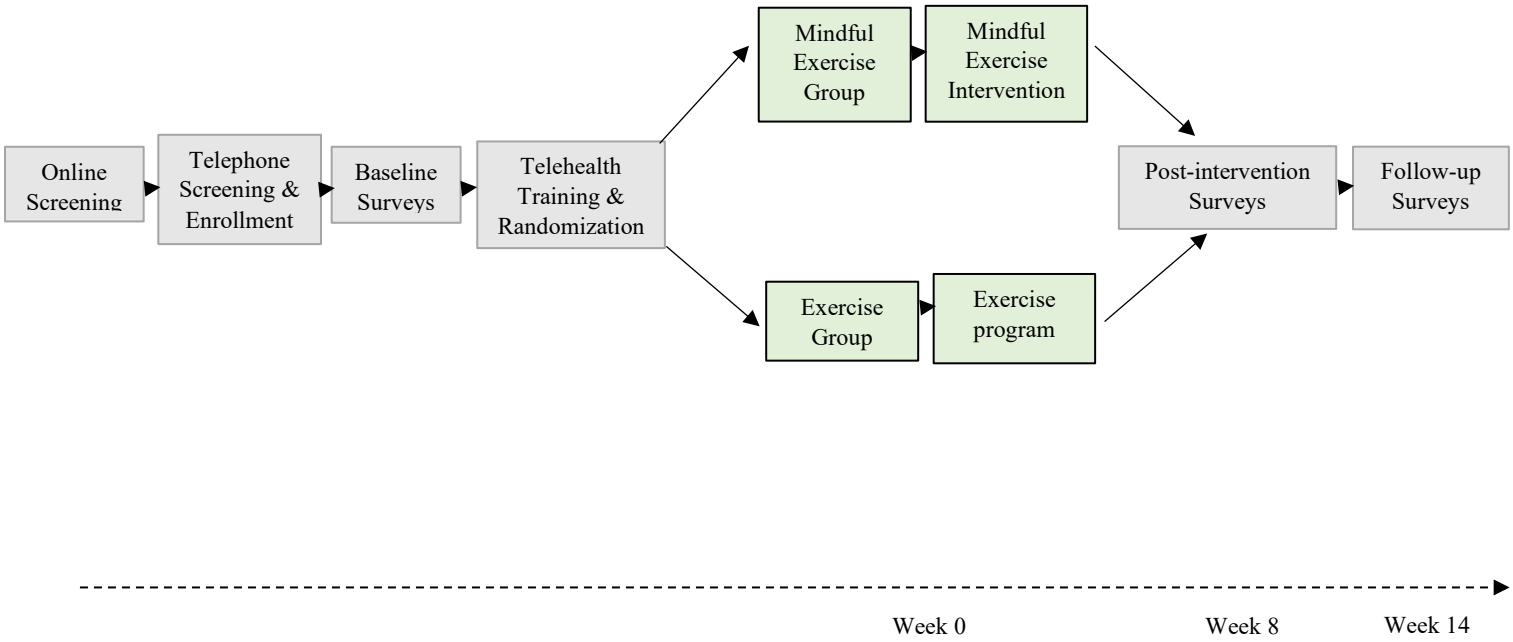


Figure 1. Study flow for participants in the study

Table 1. Schedule of Study Visits and Measurements

Week	~ -3	-2	-1	0	1	2	3	4	5	6	7	8	9-13	14
Visits			BV-R	RTT								W8-R		W14-R
Telephone Screening	X													
Consent and Enrollment	X													
Randomization				X										
Exercise Program					X	X	X	X	X	X	X	X		
Mindful Exercise Program					X	X	X	X	X	X	X	X		
Attendance to sessions					X	X	X	X	X	X	X	X		
Weekly Surveys					X	X	X	X	X	X	X	X	X	X
HEAL Treatment Expectancy				X										
eHEALS				X										
A-REALM				X										
Demographics			X											
Knee OA history			X											
Treatment History			X											
Treatment History – follow-up												X		X
Comorbidity			X											
Access to health technology			X											
PHQ-8			X									X		X
ASES			X									X		
PEG			X									X		X

Pain Survey	WPI			X									X		
	Catastrophizing			X									X		
	Homunculus			X									X		
	PainDETECT			X									X		
KOOS				X									X		X
NRSna				X											
NRSna – Follow-up													X		X
CAMS-R				X									X		X
PGA-OA				X									X		X
FABQ-PA				X									X		
CPSES				X									X		
PGIC													X		X
Feedback survey													X		
TUQ													X		
Satisfaction Scale													X		
Individual interviews													X		

BV-R: Remote Baseline Visit

RTT: Remote Randomization and Telehealth Training Visit

W8-R: Remote Post-intervention Visit

W14: Remote Follow-up Visit

BMI = Body Mass Index

eHEALS = ehealth Literacy Questionnaire

A-REALM = Arthritis-Adapted Rapid Estimate of Adult Literacy in Medicine

PHQ-8 = 8-item Patient Health Questionnaire

ASES = Arthritis Self-Efficacy Scale

PEG = Pain Enjoyment General Activity Survey

WPI = Widespread Pain Index

KOOS = Knee Injury and Osteoarthritis Outcome Score

NRSna = Numeric Rating Scale for nominated activity

PROMIS Sleep = Patient-Reported Outcomes Information System measuring sleep quality and sleep disturbance

CAMS-R = Cognitive and Affective Mindfulness Scale – revised

MOOES = Modified Outcomes of Exercise Expectations Questionnaire

PGA-OA = Patient Global Assessment of Osteoarthritis

FABQ-PA = Fear Avoidance Beliefs about Physical Activity

CPSES = Chronic Pain Self-Efficacy Scale

PGIC = Patient Global Impression of Change

TUQ = Telehealth Usability Questionnaire

AE/SAE = Adverse Event/ Severe Adverse Event

Table 2. Schedule of Optional In-Person Visit Procedures and Measurements

Week	-6 to -3	-2	-1	0	1	2	3	4	5	6	7	8
Visits			BV-I	RTT	Intervention							W8-I
BMI, BP, and Wearable Sensors												
BMI Screening	X		X									
Height			X									X
Weight			X									X
Blood Pressure			X									X
Placement of lumbar-worn sensor for physical activity			X									X
3-sensor IMU system			X									X
Knee OA physical examination			X									X
Functional Tests												
7-meter walk test			X									X
Five-times-sit-to-stand test			X									X
6MWT			X									X
SCT			X									X
Strength Tests												
Knee Isometric Extension			X									X
Knee Isometric Flexion			X									X
Quantitative Sensory Testing												
QST (PPT, TS, CPM)			X									X
EIH			X									X
Brain Function Testing (fNIRS)												

Baseline (Resting)			X									X
Serial 7			X									X
Normal Walking			X									X
Dual-task Walking			X									X
Step-up			X									X
Sub-maximal isometric knee extension exercise			X									X
Electromyography			X									X

BV-I: Optional In-person Baseline Visit

RTT: Remote Randomization and Telehealth Training Visit

W8-I: Optional In-person Post-intervention Visit

BMI = Body Mass Index

BP = Blood Pressure

IMU = Inertial Measurement Unit

6MWT = 6-meter walk test

SCT = Stair Climb Test

QST = Quantitative Sensory Testing

PPT = Pressure Pain Threshold

TS = Temporal Summation

CPM = Conditioned Pain Modulation

EIH = Exercise-Induced Hypoalgesia

3. Recruitment and Eligibility

3a. Recruitment Strategies

Participants will be recruited through multiple channels. We will use TrialFacts (https://trialfacts.com/) for data-driven recruitment via social media. Trialfacts will prepare a study site, online pre-screening form, and recruitment material for social media. Other recruitment strategies will include:

- Flyers: IRB approved flyers will be placed at various approved locations on BU/BUMC campuses, primary care practices, senior centers, and other places where potential participants might congregate
- Online advertisements (e.g., Craigslist, Lab website, etc.)
- Seminars and recruitment sessions at senior centers, churches, and other sites where older adults gather
- Mass mailing: Mass mailing will be considered if additional recruitment strategies are needed to meet accrual goals

3b. Eligibility Criteria

Inclusion Criteria

- Meet National Institute for Health and Clinical Excellence clinical guidelines for knee osteoarthritis (i.e., age $\geq$ 50 years, presence of activity related pain, presence of morning knee stiffness $\leq$ 30 minutes)
- BMI<40
- Knee pain on most days for 3 months or more
- Average overall knee pain severity of $\geq$ 4 on a 11-point numeric rating scale during previous week
- Able to attend remote sessions
- Can speak and understand English at a sufficient level to understand the study procedures and informed consent.
- Available for study duration

Exclusion Criteria

- Contraindications to exercise
- Other pain in lower back or legs that is greater than knee pain
- Received physical therapy treatment for knee OA in the past 6 months or currently receiving physical therapy
- Received any mindfulness programs such as Tai Chi, meditation, etc. in the past 6 months or currently receiving such program
- 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)
- Participation in another clinical trial for any joint or muscle pain

- Suspected or known drugs or alcohol abuse
- Wrist fracture in both wrists within past 6 months (exclusion applies only to PPT testing)
- Myocardial infarction within the past 6 months (exclusions applies only to CPM testing)
- History of Raynaud's syndrome, active vasculitis, or peripheral vascular disease. (exclusions applies only to CPM testing)
- History of lymphedema, Takayasu's arteritis, or arteriovenous fistula for hemodialysis in both arms (exclusion applies only to CPM testing)
- Mini-mental state examination (MMSE) score < 24 (only applies to optional brain function testing testing)

3c. Screening Process

Overview of the screening process

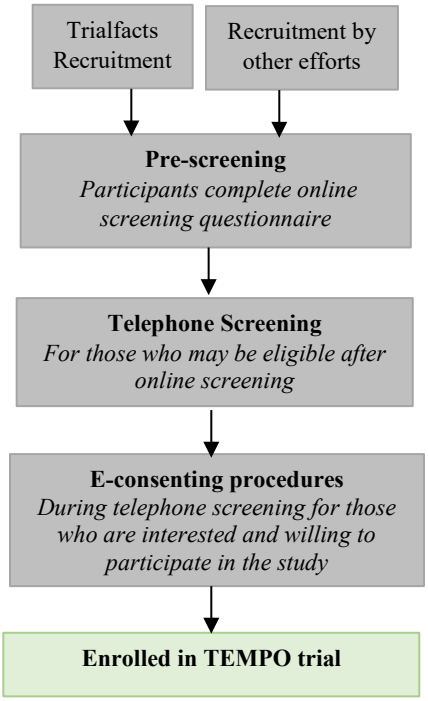


Figure 2: Screening procedures

Participants, recruited by Trialfacts and other recruitment efforts, who pass the online pre-screening form will be given a telephone screening call by a research assistant. This phone call will provide the participant detailed information about the study including goals, interventions, and participant expectation in terms of intervention and research visits. This call will also be used as an opportunity to ask clarifying questions to review eligibility of the participant. During this phone call, participants who are interested in participating in the study will undergo e-consenting procedures through REDCap database. Once the participant has electronically signed the consent form, the research assistant will sign the consent form. A copy of the consent form with both the participant and the research assistant's signature will be sent to the participant's email. A copy of the signed consent form will be saved on the lab's server for study documentation.

4. Research Visits

The proposed study is an18-week feasibility study. There are a total of four remote research visits. These include a remote baseline (week 0), post-intervention (week 8), follow-up (week 14), and individual interviews at week 8 only for participants in the mindful exercise group. Participants who opt-in for the in-person visits will make two in-person visits to Boston University. Apart from these research visits, participants will be administered a weekly survey that will document their pain and activity levels. The weekly survey will be administered throughout the 18-week study period. An overview of these visits along with compensation for each visit is shown in the table below.

Table 4. Overview of research visits

Visit	Week	Type of visit	Duration	Payment
Remote Baseline Visit	2-4 weeks before start of treatment	Remote	30 min	$25
[OPTIONAL] In-person Baseline Visit	2-4 weeks before start of treatment	In-person at Boston University	4 hours	$50
Remote Randomization and Telehealth training visit	Two to four weeks prior to intervention sessions	At-home using telehealth	45-60 minutes	[redacted]
Remote Treatment visits	Over 8-weeks (once a week)	At-home using telehealth	1 OR 2 hours per visit	
Remote Weekly Survey	Each week during treatment	At-home using email	5 min each week	
Remote Week 8 visit	At end of treatment	Remote	30 min	$25
[OPTIONAL] In-person Week 8 visit	At end of treatment	In-person at Boston University	4 hours	$50
Remote Individual Interview ***(only for participants in mindful exercise group)***	At end of treatment	At-home using telehealth	1 hour	$25
Remote Week 14 surveys	6 weeks after end of treatment	At-home using email	30 min	$25

4a. Remote Baseline Visit

The signed consent form from both participant and researcher will trigger the Automatic Survey Invitation (ASI) for remote baseline surveys on REDCap. Participants will be asked to complete the baseline surveys before they attend the telehealth training visit. Fifteen surveys collecting self-reported pain, function, and psychological health measures will be collected at this time point.

4b. In-person Baseline Visit (OPTIONAL)

Eligible participants who are interested in the study will be given an option to participate in in-person baseline visits if they are able to travel to the visit location (SAR 524, 635 Commonwealth Ave, Boston, 02215). During this visit, tests to measure their physical function, muscle strength, sensitivity to painful stimuli, and brain activity using fNIRS will be conducted (described below). Participants who agree to baseline in-person visit will be required to make the post-intervention in-person visit.

Knee Examination: A standard clinical exam of the knee that is typically used in physical therapy clinics will be performed. This includes assessment of knee tenderness, and visual assessment of knee alignment.

Functional testing: These include four standardized examinations similar to those performed in general outpatient physical therapy. Small sensors will be placed on the legs and trunk before the tests. These sensors will record their movements. These tests include tests of speed, balance, and movement control.

1. *7-meter walk test*: Walking back and forth over 7 meter (x2)
2. *Stair climbing test:* Ascending and descending a flight of stairs (x2)
3. *6-minute walk test (6MWT):* Walking for 6 minutes (x1)
4. *Sit to stand test*: sit to stand from chair (x5)

Quantitative Sensory Testing (QST): This series of tests will allow us to measure pain sensitivity: pressure-pain threshold (PPT), temporal summation, and conditioned pain modulation.

Strength testing: We will measure the strength of their leg muscles by asking them to provide maximal muscle contraction against a resistance. This testing will be done using a dynamometer commonly used in physical therapy clinics.

Brain function test: Participants will first complete the Mini-Mental State Examination survey (MMSE) to determine eligibility for the optional brain function testing using fNIRS. Only participants who meet the MMSE criteria and agree to brain function testing will undergo these procedures. Participants will wear a wireless fNIRS device (NIRSport, NIRx, Medical Technologies) with 30 channels. 10 sources and 12 detectors over their scalp surface of bilateral prefrontal cortex (i.e., forehead). Four surface electromyography sensors will be attached around their knee joint muscles. For the test, participants will wear the device and sensors and complete walking, dual-task walking, step-up, and sub-maximal strengthening exercise to investigate the cortical function and movement patterns during these activities.

4c. Remote Randomization and Telehealth Training Visit

After the baseline visit testing procedures are completed, participants will meet with a research assistant in a remote randomization and telehealth training visit. At the visit, participant attendance and fidelity of the telehealth training visit will be documented in “Telehealth Training Visit Tracking” form on REDCap.

Randomization procedures

A randomization list will be generated by study biostatistician and will be stratified by sex. This provides an assignment that the study staff has no control over the randomization process and that each participant has an equal chance of being assigned to either group. These group assignments will be pre-specified and placed in sealed envelopes unmarked except for an envelope number (TEMPO1## or TEMPO2##) on the outside. Envelopes with numbers starting with the number 1 (e.g., TEMPO1##) will be for male participants and those starting with the number 2 TEMPO 2## will be for female participants. For participants who opted-in for the in-person baseline visit, the randomization procedures will occur in-person after the baseline data collection procedures have been completed.

Below is a script that the research assistant will use for the randomization procedures

4d. Post-Intervention (Week 8) Visit

The weekly attendance of the participants will be tracked on an Attendance Survey on REDCap. The completion of the 8th session will trigger the ASI for the post-intervention remote surveys. Participants will receive a total of 15 surveys, including self-reported pain, function, and psychological measures collected at baseline and feedback and satisfaction surveys. Those who opted in for the in-person baseline visit will be invited for the in-person post-intervention visit.

4e. Follow-up (Week 14) Surveys

Six weeks after the end of the 8-week intervention, participants will be administered six surveys related to their knee pain, function, perceived impression of change, and psychological measures.

4f. Weekly (Week 1-14) Surveys

All participants will be administered a short weekly survey starting from the start of the intervention (week 1) to the follow-up period (week 14). This weekly survey will include a question related to pain in a specific activity selected at baseline and will also include home exercise, physical activity, and medication log. For those assigned to the mindful exercise group, additional questions related to mindfulness and mindful exercise log will be included. The weekly survey will be administered by email using automated survey reminders in REDCap.

4g. Individual Interviews (Week 8)

At the end of the 8-week interventions, participants from the mindful exercise intervention will be invited for individual interviews. The interviews will be conducted over Zoom by a professor who is an expert in qualitative methods and who was not involved in any other study procedures. The interview guide will be theoretically informed based on the Theoretical Framework of Acceptability(1). The interviews will be audio-recorded on Zoom and transcribed verbatim and de-identified by GMR transcription services in Boston.

5. Interventions Description, Overview, Objectives

5a. General Overview

Two days before the first intervention session, participants will receive a reminder email informing them of the date, time, and zoom link of the intervention session. This information will also be provided in the manual given to them at the baseline visit**.** One day before the intervention session, participants will receive a call from the research assistant reminding them of the first intervention session.

Participants in both groups will receive 8 telehealth, group-based, supervised intervention sessions. Participants in the exercise group will receive evidence-based strengthening and neuromuscular exercises for the knee for 12-weeks. Participants in the mindful exercise group will receive the same exercises but they will be trained on performing the exercises mindfully. The interventions will be conducted in two waves.

5b. Interventions

Interventions will be delivered in a group setting in two waves over 8-weeks. Once at least 12 people are recruited, interventions for wave 1 will commence. Recruitment and randomization processes will be ongoing while interventions for wave 1 participants are in progress. Once 40 participants are randomized, recruitment will cease and the interventions for the second wave of participants will commence.

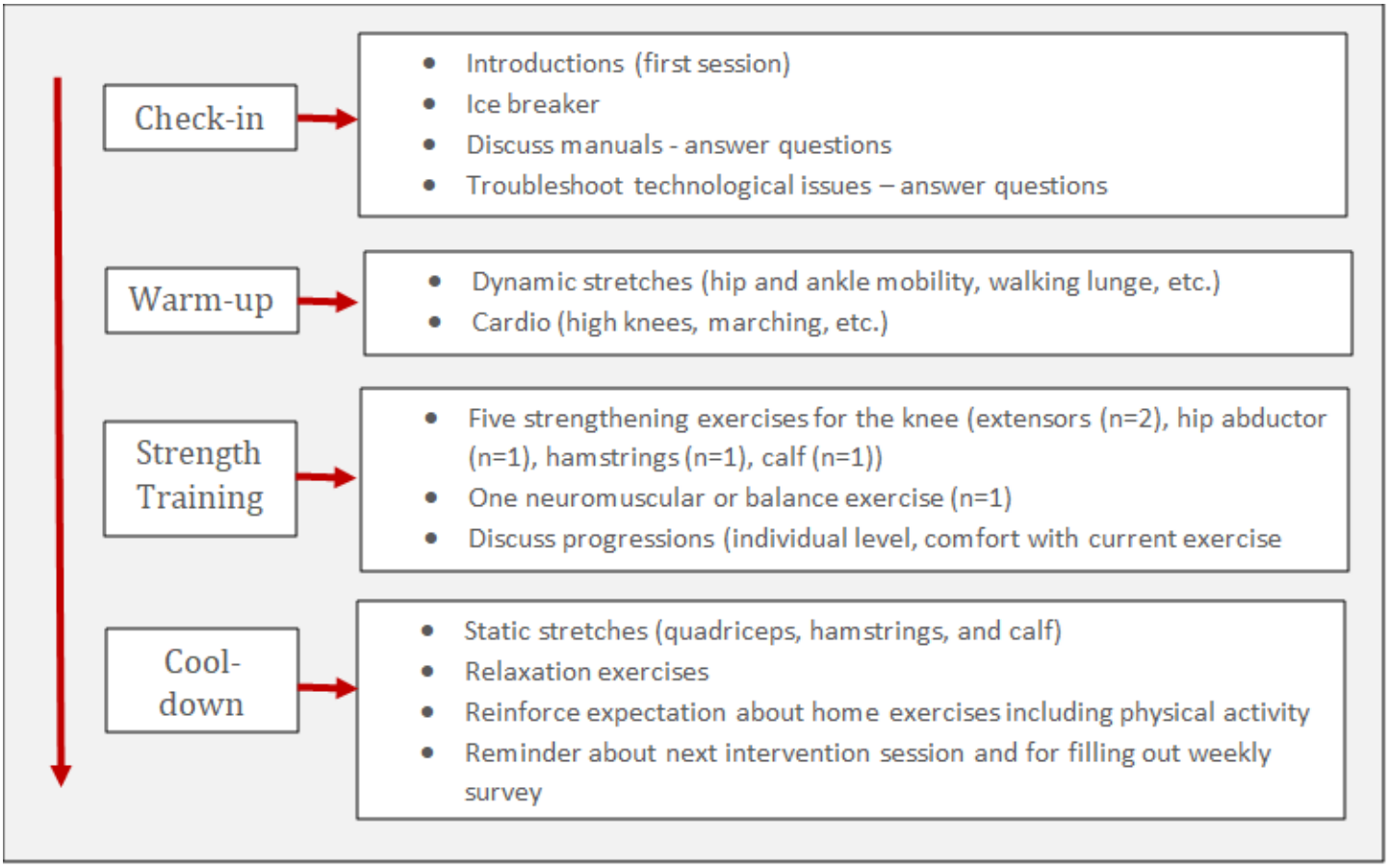
Interventions in both mindful exercise and exercise groups will be delivered in a group setting via HIPAA-protected Zoom videoconferencing software. Along with the interventions below, participants in both groups will receive educational materials each week via email (Table 5), a program manual that contained information about study tasks and interventions, and a set of resistance bands and a step-up platform with adjustable height. After the end of the 8-week interventions, participants were asked to continue to practice on their own for another 6 weeks.

Table 5. Weekly educational material for participants in both groups

Week	Topics
Week 1	Knee osteoarthritis overview and self-management
Week 2	Pain education
Week 3	Physical activity, exercise, and weight management
Week 4	Reducing knee joint loading
Week 5	Complementary and alternative therapies for knee osteoarthritis
Week 6	Pharmacological therapies for knee osteoarthritis
Week 7	Managing osteoarthritis with comorbidities
Week 8	Surgical treatments for knee osteoarthritis

5b.1. Exercise Sessions

The session overview for the exercise program is shown below:



The exercise intervention will be delivered and supervised by a physical therapist. Each one-hour session will include dynamic stretches for warm up, 5-6 lower extremity strengthening exercises, 1-2 neuromuscular exercises, and static stretches for cool down (Table 6). Each exercise will be performed bilaterally in three sets of eight repetitions. Participants will monitor their own progressions based on the Modified Borg RPE scale. To facilitate the self-progressions, they will be provided with options to modify each exercise to make it either easier or more challenging. For home exercises, participants will be instructed to perform strengthening exercises at least two other days a week and aerobic exercise of their choice at least five days a week.

Table 6: List of supervised exercises performed during the telehealth sessions

Goals	**Exercises:** *Each session included 6-8 of the following exercises.* *All exercises were done in 3 sets of 8 repetitions*
Strengthening	
Knee Extensors	Seated knee extension
	Standing terminal knee extension
Knee Flexors	Leg Curls
Hip Extensors	Back leg raises
Hip Flexors	Forward leg raises
Hip Abductors	Side leg raises

Hip Adductors	Standing hip adduction
Calf muscles	Heel raises
Balance	Heel/toe walking
Neuromuscular	Step ups
	Wall squats
	Air squats
	Partial/deep forward lunges
	Partial/deep backward lunges

Exercise Progressions: All participants will be expected to monitor their own progressions. For this, information regarding the appropriate intensity of exercise (4-6 range on the Modified Borg's RPE Scale)[117] will be provided to them in their home exercise manuals. During the exercise sessions, participants will be given options (and shown video demonstration of options) for making the exercise easier or more challenging so that they can stay within the range of 4-6 on the RPE scale. During the intervention sessions, the participant will be given constant reminders of the desired exercise intensity and the interventionist will answer any questions the participant might have regarding their level of exercise performance.

5b.2. Mindful Exercise Sessions

The mindful exercise intervention will be delivered jointly by a physical therapist (NS) and a mindfulness instructor with ~ 20 years of experience. Along with the exercises, participants in the mindful exercise group will training in mindfulness in the first 3 sessions (Table 7). Starting from session 4, participants will be instructed to integrate mindfulness into their exercise movements. Each session will be ~ 2 hours in length roughly divided into four 30-min blocks. In the first and third 30-min blocks, participants will practice concepts of mindfulness meditation wherein they will be trained to develop non-judgmental moment-to-moment awareness using either breath, body sensations, or counting as an anchor. In the second and the fourth 30-min blocks, participants will perform the same exercises as those provided to the exercise group. However, participants in this group will perform the exercises mindfully, i.e., they will use either breath, body sensation, or counting as an anchor while performing exercise movements. Participants in this group will receive same instructions as the exercise group for home exercise. Furthermore, participants in this group will be advised to practice mindfulness for at least 20-minutes each day and to practice mindfulness during exercise and physical activity.

Table 7: Meditations in the Mindful Exercise program

Sessions and Goals	Meditations
Session 1	
Raisin meditation	Training on how to separate senses of observation, touch, sound, and feel
Awareness of breath meditation	Training on how to use breath as an anchor
Session 2	
Body scan meditation	Training on how to use body sensation as an anchor
Breath and counting meditation	Training on how to use counting as an anchor
Session 3	
Moving meditation	Introducing how to combine movement and mindfulness
Body scan meditation	Practice on how to use body sensation as an anchor
Mindful exercises	Combining exercise and mindfulness
Session 4	
Breath and counting meditation	Training on how to exercise using either the breath, counting, or body sensation as an anchor
Walking meditation	Combining movement and mindfulness

Mindful exercises	Combining exercise and mindfulness
Session 5	
Awareness of breath meditation	Practice on how to use breath as an anchor
Mindful exercises	Combining exercise and mindfulness
Session 6	
Awareness of breath meditation	Practice on how to use breath as an anchor
Body scan meditation	Practice on how to use body sensation as an anchor
Mindful exercises	Combining exercise and mindfulness
Session 7	
S.T.O.P meditation (S=sit down, T=take a breath, O=observe, P=proceed with day)	Training on incorporating mindfulness in daily life
Pain-focused meditation	Training on how to detach from difficult sensations
Mindful exercises	Combining exercise and mindfulness
Session 8	
Review and summary	A summary and practice of what was covered in the 8-week program and practice of aware of breath and body scan meditations
Mindful exercises	Combining exercise and mindfulness

7. Statistical Analysis Plan

The following outcome measures will be used to determine feasibility of the telehealth interventions in this study.

a) Recruitment: Proportion of participants successfully contacted who agreed to participate in the study over 6-months

b) Attendance: Proportion of sessions attended

c) Retention: The percentage of participants who complete the post-intervention surveys at the end of the study period (12-weeks)

The number of safety events, and data for recruitment, attendance, and retention will be reported descriptively. Aggregate data for intervention adherence at home as well as feedback from the participants will be reported. For other PROs, within group changes and differences between groups along with 95% confidence intervals will be reported. Data will be reported using an intention-to-treat approach with data from all randomized participants included. Missing data will not imputed.

8. Safety Reporting

AEs, SAEs, and Unanticipated Problems Definitions

Adverse event (AE) is any unfavorable or unintended diagnosis, sign (including abnormal laboratory finding), symptom, or diseases temporarily associated with the study intervention, which may or may not be related to the intervention. AEs include any new events not present during the pre-intervention period or events that were present during the pre-intervention period but have increased in severity.

Serious adverse event (SAE) is any AE that results in any of the following outcomes:

- Death,
- Life-threatening adverse experience,
- Inpatient hospitalization or prolongation of existing hospitalization,
- Persistent or significant disability/incapacity,
- Congenital anomaly/birth defect, or cancer, or any other experience that suggests a significant hazard, contraindication, side effect or precaution that may require medical or surgical intervention to prevent one of the outcomes listed above,
- Event that changes the risk/benefit ratio of the study.

An unanticipated problem is any incident, experience, or outcome that meets ALL of the following criteria:

- Unexpected in terms of nature, severity, and frequency, given the research procedures that are described in the protocol related documents the characteristics of the subject population being studied
- Related or possibly related to a subjects participation in the research study, and
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) related to the research than was previously known or recognized.

8a. Event Notification

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 if any events have occurred prior to each intervention or testing session and to report all activity-related symptoms of pain or discomfort to the investigator or research team member, 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.

Because this study's procedures pose relatively low risk to participants, weekly 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. Study staff will report non-serious AEs to the PIs within 7 days.

Study staff will report SAEs to the PI and the research assistant as soon as they are made aware of the SAE. All research personnel who have contact with study participants are responsible for reporting to appropriate study personnel all events directly observed or reported by the study participant. When necessary, additional details of an event should be obtained by the participant's outside/personal clinician or PCP.

Once the PI and research assistants are notified of the event, the following steps will be taken:

1. The PI will determine if the event is a SAE or an event or problem that is unanticipated (in terms of nature, severity, or frequency, related or possibly relate) and suggest that there is an increased risk to subjects or others than was previously known
2. If the event is an SAE refer to section 8a.1
3. If the event or problem is unanticipated and meets all of the above criteria (unexpected, related to the study, and increases risk) refer to section 8a.2
4. For all events or problems, the research assistants will begin the AE/SAE form under the appropriate participant and fill in the relevant information. This form should be completed once the research assistant is made aware of the event and more information can be completed as the event unfolds. The information from this form can be used in the report to IRB when appropriate.

5. The PI is responsible for making the final decision regarding attribution of the AE to study and the severity of the AE (mild, moderate, or severe).

8a.1. Reporting to IRB

The IRB is responsible for ensuring compliance with federal regulations and state laws for the protection of the rights and welfare of human research participants. The following events must be reported to the IRB within 5 working days of discovery:

1. Death of a research subject if the death is related or possibly related to the research study.
2. Adverse events that are unanticipated (in terms of nature, severity, or frequency, related or possibly related, and suggest that there is an increased risk to subjects or others than was previously known.
3. Any event or problem that is unanticipated (in terms of nature, severity, or frequency, related or possibly relate) and suggest that there is an increased risk to subjects or others than was previously known
4. Breach of confidentiality
5. Suspension or termination of the research study by the research assistants or PI
6. Incarceration of a research subject enrolled into the study
7. Study staff misconduct
8. Medication or laboratory error regardless of whether subjects experienced harm
9. New information (e.g. interim analysis, safety monitoring report, publication, or other finding) that suggests that there are new or increased risks to subject or others
10. A complaint by a research subject or others that suggests that rights, welfare, or safety of a subject has been adversely affected.
11. Any other problem that suggests that the research places subjects or others at an increased risk for harm or adversely affects the rights, welfare or safety of subjects or others.

The research assistant will draft the event form based on the REDCap AE/SAE form and send it to the PI's who will review and submit the form to the IRB within 5 working days upon discovery.

Any events or problems that occur that do not meet the above criteria will be tracked and recorded through REDCap AE/SAE's forms for the individual participant. Any non-serious events will be discussed at our weekly lab meetings. Those events will be reported to the IRB at the next continuing review period.

8a.2. Events Occurring at Interventions

Any events occurring before, during, or after an intervention will be reported in the following way:

1. If an event meets the definition of an SAE or the IRB's criteria, the above steps will be taken to meet the reporting requirement for the IRB. In addition, the clinician will participate in helping with the event narrative and follow up measures within their scope of practice.
2. For all events involving the exercise or mindful exercise interventions, the interventionists will notify the study team of the event. The research assistant will create the AE/SAE report on REDCap using the interventionist's notes in the adverse event form on REDCap.
3. Events that do not meet the timely reporting requirements (i.e. 5 working days IRB) will be tracked and reported at the continuing review.

8b. Data and Safety Monitoring Activities

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. Trained research assistants will perform sensor placement and monitor participants during the experimented procedures. The research procedures in this study are 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.

8c. Protocol Deviation

This section of the MOOP describes relevant deviations/violations and the reporting process to appropriate parties. Deviation is defined as any change or alteration to the IRB-approved protocol without prospective IRB approval. A protocol deviation is any occurrence that is not in compliance with the approved study protocol, IRB policies, federal regulations, or any other applicable regulations.

Major Deviation

Major Deviation is defined as any change or alteration that has the potential to:

- Adversely affect the rights, welfare or safety of the participants,
- Adversely affect the integrity of the research data, or
- Affect the participant's willingness to participate.

Major deviations should be reported to the IRB within 5 working days.

Minor Deviation

Minor Deviation is defined as any change or alteration that has not or does not have the potential to:

- Adversely affect the rights, welfare or safety of the participants,
- Adversely affect the integrity of the research data, or
- Affect the participant's willingness to participate in the study.

Minor deviations should be reported to the IRB within 20 working days. To report deviations to the IRB the project manager will draft an Event Form. The investigator is responsible for making an initial determination of whether the deviation is major or minor. The PI must additionally report deviations/exceptions to [ ] during the bi-monthly project management meetings. The research assistants will maintain a log of all protocol deviations/violations on SharePoint under Adverse Event and Protocol Deviation Folder.

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