PROTOCOL FOR NON-EXEMPT RESEARCH INVOLVING HUMAN SUBJECTS

Title:	Use of a Self-Guided Mindfulness Mobile Application to Improve Pain Outcomes in Individuals with Knee Osteoarthritis
IRB #:	FWH20190033H

Principal Investigator (PI)	Rank / Civ Rating	Branch	AD/DoD Civ/ Ctr/Civilian	Dept/Base	Phone #	E-mail
Jillian Sylvester, MD	Capt	USAF	AD	FMR/ Scott AFB	(919) 244-1854	jillian.e.sylvester2.mil@mail.mil

The research relevance of this protocol focuses on:	☒	**Treatment**

Does the research fall under the purview of any other departments or committees?	No
Radiation Safety Committee	☒
Institutional Biosafety Committee or Biosafety Officer	☒
59th Medical Wing (59 MDW) Office of Research and Technology Applications (ORTA)	☒
59 MDW/SGARB Resource Management Office	☒

1. LOCATION AND SPONSOR

Collaborating Facilities: None

AF Sites Seeking Regional IRB:

Nellis AFB (99MDG): Capt Matthew Hess, matthew.c.hess7.mil@mail.mil, (801) 698-5008
Scott AFB (375MDG): Capt Jillian Sylvester, jillian.e.sylvester2.mil@mail.mil, (919) 244-1854
Travis AFB (96MDG): Capt Alexander Knobloch, alexander.c.knobloch.mil@mail.mil, (309) 631-0046

Study Sponsors: None

2. RESEARCH PLAN

Purpose of Study:

This study will investigate if mindfulness training via a smartphone mobile app is effective in improving OA-related knee pain.

Hypotheses, Research Questions, or Objectives:

- Objective 1: Test whether use of a mindfulness mobile app improve knee pain in adults with knee OA among active duty and other DoD beneficiaries.
- Objective 2: Evaluate if self- reported, health-related quality of life and mindfulness scores predict response to mindfulness treatment in OA.
- Null Hypothesis 1: A mindfulness mobile app has no effect on knee pain in adults with knee OA.
- Alternative Hypothesis 1: A mindfulness mobile app improves knee pain in adults with knee OA.
- Null Hypothesis 2: Self- reported, health-related quality of life and mindfulness scores have no effect on response to mindfulness treatment in OA.
- Alternative Hypothesis 2: Self- reported, health-related quality of life and mindfulness scores predict response to mindfulness treatment in OA.

Significance:

Osteoarthritis (OA) is a major cause of disability in the United States and is expected to affect 26% of Americans by 2040[5, 9]. Studies of the socioeconomic burden of OA demonstrate a 2-4 fold increase in healthcare expenditures for people with OA as compared to non-affected controls[24, 25]. In addition, associated healthcare costs continue to rise: recent estimates of insurer and out of pocket healthcare costs of osteoarthritis exceed $185 billion USD per year with another $10 billion lost from absenteeism at work[13].

Knee OA is one of the most commonly encountered diagnoses in the study team's sports medicine clinics. Despite the commonality of this condition, effective therapies are lacking as recent studies have called standard of care interventions into question, including NSAIDs, injectable, and surgery[17, 20, 21]. As a chronic, progressive disease, the management of OA centers on maximizing function while controlling pain. Conservative treatment options center on self-treatment modalities of therapeutic exercise programs (initiated through Physical Therapy), regular exercise, and weight control. Use of a mindfulness application may be another potential avenue of treatment. As the incidence of osteoarthritis rises, so does the projected physician shortfall. By 2030, this projected shortfall will reach 7,300-43,100 doctors[10], highlighting the need for increased use of patient self-treatment modalities. There is a gap in the literature investigating the potential use of a mobile health application ("app")

as a biopsychosocial intervention to achieve improvement in knee pain, an approach that could be packaged readily for use in a clinical setting.

Military Relevance:

Osteoarthritis is a leading cause of pain and disability among adults worldwide; it is a very common and expensive ailment afflicting Active Duty and Retired Service Members as well as their dependents. Military members are more likely to experience osteoarthritis than their civilian counterparts, and the overall incidence of OA is rising in the military population, particularly among individuals nearing retirement. This study explores an inexpensive, noninvasive, self-directed treatment adjunct that may help better manage osteoarthritis-associated pain. Such a treatment may help to decrease costs associated with osteoarthritis disease management.

Background and Review of Literature:

Osteoarthritis (OA) is a progressive, degenerative joint disease and a leading cause of morbidity and disability worldwide[5]. OA is estimated to affect 54.4 million adults, though recent studies suggest this commonly accepted number is greatly underestimated[11]. Knee OA is the most common form of OA, and studies estimate that approximately 7% of Americans older than 25 (or 14 million people) have symptomatic knee OA[6]. The lifetime risk of developing symptomatic knee OA is 45%[18].

There is a well-established bidirectional relationship between OA and mental health that suggests a role for biopsychosocial intervention in management of OA. The practice of mindfulness, classically defined by Kabat-Zinn as "the awareness that emerges through paying attention on purpose, in the present moment, and non-judgmentally to the unfolding of experience moment by moment", may be an effective treatment for chronic pain[12]. Studies of in-person mindfulness training have been shown to improve pain outcomes in those with both nonspecific and specific chronic pain, including pelvic pain and low back pain[8, 14,15,22,23]. In addition, mindfulness interventions have proven effective adjunct treatments for mood disorders, fibromyalgia, rheumatoid arthritis, and stress reduction in otherwise healthy patients[3, 4, 26, 27]. A recent systematic review of 13 randomized control trials found that mindfulness training improved patients' perception of chronic pain and overall quality of life, suggesting it may be an effective adjunct treatment in the multidisciplinary approach to treatment of chronic pain[2]. Regarding our specific population, a study of individuals with knee OA demonstrated that those with greater baseline mindfulness exhibited an improved self-perception in their physical quality of life and appeared to decrease the effect of pain on stress[15]. In this same study group, those with higher total mindfulness scores were found to have a 38% greater response to a 12-week physical intervention (Tai Chi or physical therapy) than those with low mindfulness scores[16]. One study found that 58% of individuals affected by OA had concomitant mental health disorder[19]; the benefit of mindfulness training may demonstrate an increased effect in those with concomitant mood disorders.

To date, mindfulness studies involving chronic pain conditions have involved manpower- intensive interventions (in-person mindfulness training, group therapy, multiple physician appointments, etc.), which are difficult to implement in busy clinical settings. Web- and mobile health applications (mHealth) may provide an effective alternative to these interventions. A 2016 systematic review of 10 web-based mindfulness training programs found that such facilitator- free interventions were effective in reducing depression and anxiety[7]. To our knowledge, only one protocol to date has been published investigating the use of a mindfulness mobile app as an intervention for improving outcomes in chronic pain[1].

Our primary aim in this study is to determine if regular use of a mindfulness application improves pain outcomes in adults with knee osteoarthritis. Our secondary aim is to determine if self-reported Healthcare-Related Quality of Life (HRQoL) scores predict response to mindfulness treatment in OA. We hypothesize that the use of an mHealth intervention for mindfulness training may be an effective adjunct treatment of chronic knee osteoarthritis pain; specifically, that regular use of a mindfulness application will result in a statistically significant reduction in pain outcomes and improvement in physical function as determined by the KOOS scoring system. We also hypothesize that those with lower baseline self-reported HRQoL scores are more likely to see a greater improvement in their pain and function with use of a mindfulness application than those with higher baseline scores.

Bibliography:

1. Ball E, Newton S, Kahan BC, *et al*. Smartphone App Using Mindfulness Meditation for Women with Chronic Pelvic Pain (MEMPHIS): Protocol for a Randomized Feasibility Trial. *JMIR Res Protoc*. 2018; 7(1):e8.
2. Ball EF, Nur S, Muhammad SE, *et al*. Does mindfulness meditation improve chronic pain? A systematic review. *Curr Opin Obstet Gynecol*. 2017;29(6):359–366.
3. Cherkin DC, Sherman KJ, Balderson BH, *et al*. Effect of Mindfulness-Based Stress Reduction vs Cognitive Behavioral Therapy or Usual Care on Back Pain and Functional Limitations in Adults With Chronic Low Back Pain: A Randomized Clinical Trial. *JAMA*. 2016;315(12):1240-9.

4. Chiesa A, Serretti A. A systematic review of neurobiological and clinical features of mindfulness meditations. *Psychol Med*. 2010;40(8):1239–1252.
5. Cross M, Smith E, Hoy D, *et al*. The global burden of hip and knee osteoarthritis: estimates from the global burden of disease 2010 study. *Ann Rheum Dis*. 2014;73(7):1323-30.
6. Deshpande BR, Katz JN, Solomon DH, *et al*. Number of Persons with Symptomatic Knee Osteoarthritis in the US: Impact of Race and Ethnicity, Age, Sex, and Obesity. *Arthritis Care Res (Hoboken)*. 2016;68(12):1743-1750.
7. Fish J, Brimson J, Lynch S. Mindfulness Interventions Delivered by Technology Without Facilitator Involvement: What Research Exists and What Are the Clinical Outcomes? *Mindfulness (N Y)*. 2016;7(5):1011-1023.
8. Fox SD, Flynn E, Allen RH. Mindfulness meditation for women with chronic pelvic pain: a pilot study. *J Reprod Med*. 2011;56(3-4):158-62.
9. Hootman JM, Helmick CG, Barbour KE, *et al*. Updated projected prevalence of self- reported doctor-diagnosed arthritis and arthritis-attributable activity limitation among US adults, 2015-2040. *Arthritis Rheumatol*. 2016;68(7):1582-7.
10. IHS Markit, The Complexities of Physician Supply and Demand 2017 Update: Projections from 2016 to 2030. Prepared for the Association of American Medical Colleges. Washington, DC: Association of American Medical Colleges. Accessed November 2018.
11. Jafarzadeh SR, Felson DT. Updated Estimates Suggest a Much Higher Prevalence of Arthritis in United States Adults Than Previous Ones. Arthritis *Rheumatol*. 2018; 70(2):185-192.
12. Kabat-Zinn J. Mindfulness-based interventions in context: past, present, and future. *Clin Psychol Sci Prac*. 2003;10(2):144–156. Kotlarz H, Gunnarsson CL, Fang H, Rizzo JA. Insurer and out-of-pocket costs of osteoarthritis in the US: Evidence from national survey data. *Arthritis Rheum* 2009; 60:3546–3553.
13. Kotlarz H, Gunnarsson CL, Fang H, Rizzo JA: Osteoarthritis and absenteeism costs: evidence from US National Survey Data. J Occup Environ Med. 2010; 52:263–268.
14. la Cour P, Petersen M. Effects of mindfulness meditation on chronic pain: a randomized controlled trial. Pain Med. 2015 Apr;16(4):641-52.
15. Lee AC, Harvey WF, Price LL, et al. Mindfulness is associated with psychological health and moderates pain in knee osteoarthritis. Osteoarthritis Cartilage. 2017;25(6):824-831.
16. Lee AC, Harvey WF, Price LL, et al. Mindfulness Is Associated with Treatment Response From Nonpharmacologic Exercise Interventions in Knee Osteoarthritis. Arch Phys Med Rehabil. 2017;98(11):2265-2273.
17. McAlindon TE, LaValley MP, Harvey WF, et al. Effect of Intra-articular Triamcinolone vs Saline on Knee Cartilage Volume and Pain in Patients With Knee Osteoarthritis: A Randomized Clinical Trial. JAMA. 2017;317(19):1967-1975.
18. Murphy LB, Schwartz TA, Helmick CG, et al. Lifetime risk of symptomatic knee osteoarthritis. Arthritis Rheum. 2008;59(9):1207-13.
19. Nazarinasab M, Motamedfar A, Moqadam AE. Investigating mental health in patients with osteoarthritis and its relationship with some clinical and demographic factors. Reumatologia. 2017;55(4):183-188.
20. Nissen SE, Yeomans ND, Solomon DH, et al. Cardiovascular Safety of Celecoxib, Naproxen, or Ibuprofen for Arthritis. N Engl J Med. 2016;375(26):2519-29.
21. Skou ST, Roos EM, Laursen MB, et al. A Randomized, Controlled Trial of Total Knee Replacement. N Engl J Med. 2015;373(17):1597-606.
22. Turner JA, Anderson ML, Balderson BH, et al. Mindfulness-based stress reduction and cognitive behavioral therapy for chronic low back pain: similar effects on mindfulness, catastrophizing, self-efficacy, and acceptance in a randomized controlled trial. Pain. 2016; 157(11): 2434-2444.
23. Veehof MM, Trompetter HR, Bohlmeijer ET, Schreurs KM. Acceptance- and mindfulness- based interventions for the treatment of chronic pain: a meta-analytic review. Cogn Behav Ther. 2016; 45(1): 5-31.
24. Wang SX, Ganguli AX, Bodhani A, et al. Healthcare resource utilization and costs by age and joint location among osteoarthritis patients in a privately insured population. J Med Econ. 2017;20(12):1299-1306.
25. Xie F, Kovic B, Jin X, et al. Economic and Humanistic Burden of Osteoarthritis: A Systematic Review of Large Sample Studies. Pharmacoeconomics. 2016; 34(11):1087- 1100.
26. Zangi HA, Mowinckel P, Finset A, et al. A mindfulness-based group intervention to reduce psychological distress and fatigue in patients with inflammatory rheumatic joint diseases: a randomized controlled trial. Ann Rheum Dis. 2012;71(6):911-7.
27. Zautra AJ, Davis MC, Reich JW, et al. Comparison of cognitive behavioral and mindfulness meditation interventions on adaptation to rheumatoid arthritis for patients with and without history of recurrent depression. J Consult Clin Psychol. 2008;76(3):408-21.

3. RESEARCH DESIGN AND METHODS

Research Design and Methods:

Male and Female active duty members and DoD beneficiaries, ages 18 to 74 years old, meeting the inclusion/exclusion criteria will be offered an opportunity to participate. They will be recruited from the clinics located at Scott AFB, Nellis AFB, and Travis AFB. All of the below items are research-related unless marked as 'standard of care':

Telephone Eligibility review: We will obtain the potential subject's permission to be contacted prior to direct contact by study staff. Those subjects who respond to advertisements or recruitment letters have implicitly given their permission to be contacted. We will contact potential subjects over the telephone to determine their initial eligibility for and interest in this research study. We will use the attached "Telephone Eligibility Script" and record responses. . For those that are interested in participating, we will retain these surveys in accordance with the storage plan outlined in this study for the duration of the study. For those not determined eligible, the surveys will be shredded.

Screening Visit:

- Obtain and document signed Informed Consent document and HIPAA Authorization.
- Review past medical history in Armed Forces Health Longitudinal Technology Application (AHLTA) to verify the inclusion/exclusion criteria including previous encounter, vital signs review, co-morbidities, demographics, problems list, confirmatory x-rays demonstrating radiographic evidence of knee osteoarthritis.
- We will ask the participants to complete the Screening Visit Medical history questionnaire.
- Record: Age at time of randomization, gender, Kellgren and Lawrence (KL) Grade score at time of enrollment, age at time of osteoarthritis diagnosis, prior knee osteoarthritis therapies to date, name of standard of care medications (over-the-counter and prescription), current email address (to be used for scheduling and weekly email reminders), height (in inches), weight (in pounds), history of prior injury to the affected knee(s), current level of exercise, physical therapy in the past year, and prior experience with mindfulness.

Randomization: Subjects will be randomized into 1 of 2 groups using block randomization with repeated measures:

- **Intervention Group:** Patient education regarding osteoarthritis, its natural history, and common treatments plus the mindfulness (intervention) app. They will be provided with a pre-paid 12-week subscription to the mindfulness application, and provided an in-person demonstration on how to use it, and the subscription license code will be recorded for the purposes of tracking use after the conclusion of the study. The intervention group will be asked to use the mindfulness app 10 minutes per day/5 days per week. To standardize Pack usage across all participants, users will be asked to complete the Headspace Essentials", "Pain Management", and "Physical Health" Session Packs.

The intervention application, Headspace, employs short, audio-guided sessions that teach the principles of mindfulness. Participants will register an account within in the application, requiring they provide their name, an email address, and a password. The application will collect usage data, tracking participants' time spent using the application and which specific mindfulness session (known as a "Pack") they used. Aggregate usage data will be provided to the study team by Headspace following the 12-week intervention period, identified only by subscription code. The study team will compare this usage data against participant self-reported use to confirm adherence to the study protocol.

- **Control Group:** Patient education regarding osteoarthritis, its natural history, and common treatments plus the My Water Balance (control) app and provided an in-person demonstration on how to use it. My Water Balance calculates an individual's recommended daily water requirements and assists users in tracking their daily fluid intake. The control group will be asked to log their water intake for the duration of the study, with requested use of 5 days per week to create an equal control. This application is free to download and use. There are options for in-app purchases and application upgrades, though users will be advised against doing so. Information logged in the application may be stored on a third party server; however, no application data will be extracted by the study team. Application use will be reported via weekly surveys, alone.

Visit 1 (Baseline, in-person visit):

- All participants will receive patient education regarding osteoarthritis, its natural history, and common treatments.
- All will receive education about the Rx3 Home Exercise Program, which serves as a physical intervention for pain management.
- All participants will be asked to perform the Rx3 Home Exercise Program 3 times weekly.

- All participants will be assigned a study ID# and will be given the on-line baseline Knee injury and Osteoarthritis Outcome Score (KOOS), Short Form-12 (SF-12), and Five Facet Mindfulness Questionnaire-15 (FFMQ-15) surveys using Google Forms or Survey Monkey.
- All participants will receive instructions per the randomization instructions above.
- All participants will be given a Medication Diary to complete on a weekly basis.

Weeks 2-11:

Participants will receive **weekly** reminders (via email) asking that they use the app throughout the week. They will also be asked to fill out a short Weekly Survey inquiring:

- Frequency and minutes used for the intervention (My Water Balance and Mindfulness app 10 minutes per day/5 days per week)
- Frequency and minutes spent performing the Rx3 Home Exercise Program in the past week (3 times weekly)
- Use of NSAIDs or other over-the-counter pharmacologic methods of pain control in the past week.

Visit 2 (Week 12, electronic contact):

Participants will complete the following surveys and asked the following questions via Google Forms or Survey Monkey. These anonymous forms will be completed via Google Forms or Survey Monkey and the results transcribed to a master excel file for centralized data tracking. Each subject will use their pre-assigned study code to record on each completed questionnaire:

- KOOS
- FFMQ15
- SF-12
- 12-Week survey to evaluate for treatment response to the Rx3 Home Exercise Program and mindfulness app intervention.
- Group 1 (intervention group): Following completion of the 12-week intervention period, participants will no longer have free access to the Headspace application.
- Group 2 (control group) will be asked to cease the use of the My Water Balance application.

Visit 3 (Week 26, electronic contact):

Participants will complete the following surveys and asked the following questions via Google Forms or Survey Monkey:

- KOOS
- FFMQ15
- SF-12
- Groups will be queried on their continued use of the Rx3 Home Exercise Program, and over-the-counter analgesic use.
- Group 1 (intervention group) will be queried on continued employment of mindfulness techniques.
- Group 2 (control group) will be queried on continued use of diet and exercise techniques.

Visit 4 (Week 52, electronic contact):

Participants will complete the following surveys and asked the following questions via Google Forms or Survey Monkey:

- KOOS
- FFMQ15
- SF-12
- Groups will be queried on their continued use of the Rx3 Home Exercise Program, and over-the-counter analgesic use.
- Group 1 (intervention group) will be queried on continued employment of mindfulness techniques.
- Group 2 (control group) will be queried on continued use of diet and exercise techniques.

Visit 5 (Week 104, electronic contact):

Participants will complete the following surveys and asked the following questions via Google Forms or Survey Monkey:

- KOOS
- FFMQ15
- SF-12Groups will be queried on their continued use of the Rx3 Home Exercise Program, and over-the-counter analgesic use.
- Group 1 (intervention group) will be queried on continued employment of mindfulness techniques.
- Group 2 (control group) will be queried on continued use of diet and exercise techniques.

Weekly survey data will be obtained using the unique participant identifier. At no time will participants use identifiable information when completing these online surveys. These surveys will be conducted using Google Forms or Survey Monkey, and the results transcribed to a master excel file for centralized data tracking. This excel file will be password protected and stored on an encrypted drive on a CAC-enabled computer in a location separate from the participant identifiable information list discussed above. Likewise, results of interval surveys at 0-, 12-, 26-, 52-, and 104-weeks will be obtained using Google Forms or Survey Monkey and identified only via participants' unique identifier.

Study participants will receive 3 reminders asking them to complete their end-of-intervention study surveys; if they do not respond, they will be removed from the study. Those who did not complete the prior set of studies will not be queried for subsequent ones. Use of the mindfulness smartphone app will subsequently be discontinued and the license terminated at the conclusion of the study.

a. Interventions and Observations:

Participants will be re-surveyed at 12, 26, 52, and 104 weeks to evaluate long-term outcomes. The primary outcome measure will be post-intervention change in Knee injury and Osteoarthritis Outcome (KOOS) pain subscale. Secondary outcomes will include the other KOOS subscale scores, FFMQ outcomes, and SF-12 self-reported mental and physical health self-assessments at these same time intervals.

b. Setting:

Active Duty members and DoD beneficiaries ages 18-74 years will be recruited at Scott AFB O'Fallon Family Medicine Residency Clinic located at 3 St. Elizabeth's Blvd, Suite 4000, O'Fallon, IL and Scott AFB Family Health Clinic on-base, David Grant Medical Center 101 Bodin Cir, at Travis AFB, and Mike O'Callaghan Federal Medical Center, 4700 Las Vegas Blvd North at Nellis AFB. No special populations (e.g., pregnant women, children, military basic trainees, prisoners, detainees) will be recruited.

c. Date(s):

February 2019-February 2022

d. Subjects:

Adults ages 18-74 with symptomatic knee osteoarthritis. All potentially eligible patients will be offered an opportunity to participate. Some patients may be patients of the PI or AI; however, they will have the research team recruit their patients to prevent any misconception of coercion or undue influence.

e. Inclusion/Exclusion Criteria:

Inclusion Criteria	• Male and female Active Duty members and DoD beneficiaries ages 18-74 years • Meet criteria for symptomatic knee osteoarthritis according to the American College of Rheumatology (pain on more than half of the days of the past month during at least one of the following activities: walking, ascending or descending stairs, standing upright, or lying in bed at night) • Demonstrate radiographic evidence of OA, with Kellgren and Lawrence (KL) Grade ≥1 as determined by Lead Site Investigator at each study location • Must have access to a smartphone with enough memory to download the app My Water Balance or the Mindfulness app
Exclusion Criteria	• Intra-articular corticosteroid injection in the 3 months prior to participation in the study. • Intra-articular hyaluronic acid/PRP injection in the 6 months prior to participation in the study • Medical condition contraindicating moderate aerobic exercise as determined by their physician • History of knee surgery in the past 6 months or previous knee arthroplasty • Inflammatory joint disease. • Current Practice of Mindfulness • Non-English-speaking • Currently pregnant or planning pregnancy over the study period • Enrollment in other clinical research study during the study period • Inability to comply with treatment protocol, including participation in the Rx3 Home Exercise Program.

f. Source of Research Material:	
Will you be using <u>private information</u> in this study?	☒Yes
If Yes	☒protected health information (PHI) held by a covered entity

Use of identifiers with private information						
Identifiers to be Used?	**Column A-** Looked at by research team	**Column B-** Recorded on enrollment log, subject list, or key list	**Column C-**Recorded on data collection tool (survey, spreadsheet, etc.)	**Column D-** Recorded on specimen containers	**Column E-** Shared w/ others not on research team	**Column F-** Stored after study ended
Names	☒	☒	☐	☐	☐	☐
Study codes linked to individuals' identities using a key only accessible by the researcher		☒	☒	☐	☐	☐
Phone/Fax Numbers	☒	☒	☐	☐	☐	☐
E-mails	☒	☒	☐	☐	☐	☐
DoD ID#	☒	☒	☐	☐	☐	☐

Coding Plan?	
Describe the method that will be used to create and assign unique study codes to data.	The unique study code will be assigned consisting of a location identifier ("S" for Scott AFB, "N" for Nellis AFB, "T" for Travis AFB), first letter of their first name, the first letter of their last name, and the last four digits of their cell phone number. The code will be placed in a Master Key of identifiable PHI/PII for each subject at each collaborating site.
Describe the method that will be used to create and assign unique study codes to specimens.	☒N/A, not collecting specimens
What is the format of the key?	☒Electronic
Who will have access to the key?	Research Coordinator at each study site.
Where will the key be stored and how will it be protected?	Location(s): Each collaborating site will maintain a Master Key of identifiable PHI/PII that will be kept in an electronic database, which will be encrypted, password protected and the access will be restricted to the Research Coordinator. The Master Key will be electronically stored separately from the coded de-identified research data. The Master Key will not be stored on any non-government or personal computers or laptops. At the conclusion of the study, the data from each site will be de-identified prior to review and analysis. Confidentiality measures: The coded research data will be kept in a locked cabinet in a locked office and only the research department has the key. The coded research data will be retained until the conclusion of the research study. Once a Final Report has been approved by the IRB, all the paper records will be de-identified and any key linking the subject to their records will be destroyed, based on AFI 33-332, "The Air Force Privacy and Civil Liberties Program" and the National Institute of Standards and Technology Special Publication (NIST SP 800-88) for the approved methods to destroy PII. The anonymized research data will not be utilized for further research activity beyond the protocol stipulations without additional IRB approval.

Complete the table.

Source of Research Material per Participant (Procedures)	**# Routine Care**	**# Research Driven**	**# Total Procedures**
Patient Education	1	0	1
Mindfulness App usage (intervention group)	0	90	90
My Water Balance (Placebo) App usage (control group)	0	90	90
Study Diary	0	1	1
Rx3 Home Exercise Program (all groups)	0	36	36
KOOS Survey	0	5	5
FFMQ-15 Survey	0	5	5
SF-12 Survey	0	5	5

g. Instrumentation:

The KOOS is a validated patient-reported outcome survey designed to assess an individual's perception of their knee pain and associated disability. The SF-12 is a validated assessment of an individual's perception of their physical and mental health-related quality of life. The FFMQ-15 is designed to provide a quantitative evaluation of mindfulness. The Rx3 (rehab, refit, return to duty) Home Exercise Program (which serves as a physical intervention for pain management) is a rehabilitation program designed to treat generalized knee pain.

4. HUMAN SUBJECT PROTECTION

Recruitment and Consent Processes:

All potentially eligible patients will be offered an opportunity to participate. Participants will be recruited from Family Medicine, Internal Medicine, Orthopedics, and Sports Medicine clinics by way of flyers in the clinic areas, hospital at large, and in community boards at public venues on post (Commissary, BX, etc.). Some patients may be patients of the PI or AI; however, they will have the research team recruit their patients to prevent any misconception of coercion or undue influence. When a potential subject is identified by the treating physician, the Research Staff will be contacted to speak with the patient directly, with prior verbal or written authorization by the patient. Hospital staff will ask the patient if they are willing to speak with the research staff and, if they agree, then the research staff will be contacted to come to the clinic and discuss the study with the potential participant. Advertisements will be posted around the base. Pregnant women will be excluded from the study as they experience a shift in their center of mass and a progressive weakening of their abdominal muscles, both of which contribute to knee pain outside the scope of this study.

Consent Processes:

Informed Consent and HIPAA authorization will be sought in advance of any screening and study-related procedures from each prospective study subject and appropriately documented in accordance with 32 CFR 219.117. Potential candidates will be notified about the study either through posted advertisements or by their healthcare provider and will be given the opportunity to consent by one of the referred study coordinators. The study coordinator will provide a written copy of the Informed Consent Document (ICD). The subject may decline to consent without prejudice. At the subjects' discretion, they may take the ICD home to discuss further with family members or another physician, prior to making a decision. If they decide they are interested in participating in the study, they can contact the research department. If the subject consents, a copy of the signed ICD and HIPAA Authorization Document will be given to the subject. No vulnerable populations are included in this research study. Subjects who cannot provide Informed Consent will not be allowed to participate. No Legally Authorized Representatives (LAR) will be utilized. Each subject will be asked to place their de-identified research data into the "Mike O'Callaghan Military Medical Center General Research Data Repository" (FWH20180064H) for future research. If the subject does not give their authorization, then the de-identified research data will be destroyed no later than 3 years following the closure.

Recruiting Service Members	Will you be recruiting service members in a group setting?	☐Yes	☒No

Participation Compensation:	
☒	Participants will not be compensated.

Assent Process: N/A

Benefits:

The primary benefit of this research on subjects is a potential improvement in their osteoarthritis-related knee pain; however, this is not a guarantee.

Risks:

Breach of confidentiality of the data is a potential risk. Every effort will be made by the study team to protect the study data. This study otherwise holds minimal risk to the participant. Given use of third party mobile applications, there are additional risks based on participants' study cohort:

Participants in Group 1 will be asked to agree to the Terms and Conditions and Privacy Policy of the Headspace application during registration. As outlined in these documents, Headspace will maintain a record of an individual's name and email address. They will also track time spent on the application, the specific mindfulness sessions or packs employed, and the

operating system upon which the app was accessed (iOS, Android, etc.). While this information is stored on an encrypted server, there is a risk of a security breach that would result in this data being compromised. Cookies may be used to store login information and remember user preferences in the application. While not a component of registration for this study, it is possible to link one's account with social media accounts such as Facebook. Linking one's social media account is not recommended and may result in compromise of more data, including Facebook profile information.

Participants in Group 2 will be asked to download and My Water Balance on their personal smart phone. This application will store screenname, email address, password of choice, gender, and weight. In addition, they may store participants' recorded intake of water. During initial application setup, the app will be denied access to users' geographic location; however, there is a risk that individual users may reverse this option and the application may store this information. This information may be stored on a third party server and is subject to security breach and loss of confidentiality.

As a free application, users will be exposed to ads and will be offered the chance to upgrade to an ad-free, paid version. All will be advised to not make any in-application purchases as a part of this study. It is possible to link use of this application to one's social media account on Facebook, Twitter, and Instagram. Doing so will allow the application to store their social media information, including username and profile contents. Users will be advised that linking one's social media account is not recommended and may result in compromise of more data.

Costs: N/A

Safeguards for Protecting Information:		
Data and Specimen Storage Plan		
How will coded or identifiable data/specimens be stored?		
☒	Paper data, including completed consent forms	The research consents and HIPAA Authorization Documents will be stored in a locked cabinet in a locked room with restricted access.
☒	Electronic data	Medical records will be annotated to reflect the subject's participation in a research study. All coded, de-identified research data will be electronically stored separately from the Master Key of identifiable patient demographics and PHI/PII at each site.
☒	Long-term storage (following completion of the study and inactivation of IRB approval)	The research data will be coded and any links to identifiable data will be destroyed (an approved shredding bin) as soon as possible as or no later than at the closure of the study. The anonymized research data will not be utilized for further research activity beyond the protocol stipulations without additional IRB approval. All de-identified research data will be maintained for 3 years following study closure.

Safeguards for Protecting Subjects Relative to Reasonably Expected Risks:

Safeguards are in place for protecting subjects and their health data. The research consents and HIPAA Authorization Documents will be stored in a locked cabinet in a locked room. Risks related to participating will be minimized, as the subjects do not have to participate or answer any question that they do not want to complete. If at any time the patient reports a side effect, they will be referred to one of the Investigators for care.

Categories of subjects	N/A

Clinical Care:

If at any time a subject experiences any injury or adverse effects, appropriate clinical care will be given or subject will be referred to appropriate provider.

Injury Compensation: N/A

Data Safety Monitoring	☒N/A – none of the situations listed above apply

5. ALTERNATIVES

Alternatives:

The alternative is not to participate in this research study and to receive standard of care.

6. DATA ANALYSIS

Data Analysis:

Outcome Measures:

To compare the effect of the mindfulness app intervention against the control: using an intention-to-treat paradigm, the two groups will be compared via one-way analysis of variance (ANOVA).

To compare the effect of a mindfulness app intervention among high and low strata of baseline pre-intervention SF-12 and FFMQ-15 scores: statistical calculation is based on the interaction effect in a 2-way analysis of variance (ANOVA) model with 5% two-sided significance level.

Sample Size Estimation/Power Analysis:

Based on the KOOS Minimal Detectable Changes in patients with knee OA of 10 with a Standard Deviation of 15, a sample size of 74 per group will have 80% power to detect such a difference based on Student's t test for independent samples with 5% two-sided significance level. Allowing for 25% dropout, the required sample size is 99 per group to accomplish the first aim.

However, to determine if high or low strata of baseline mindfulness affects pain outcomes, a sample size of 144 per group (72 in each SF12 stratum) will have 80% power to detect a difference of 10 points with a standard deviation of 15 points (i.e., no mindfulness effect in the high SF12 stratum vs. a 10-point mindfulness effect in the low SF12 stratum). Allowing for the aforementioned 25% dropout rate, we anticipate 180 participants per group or 360 total participants.

Statistical Analysis:

Using an intention-to-treat paradigm, the first primary aims will be statistically compared via one-way analysis of variance (ANOVA). The second primary aim will be statistically compared via two-way analysis of variance (ANOVA).

Missing primary outcome data will be acknowledged in the overall report of analysis. The primary outcome data is based on KOOS scoring system. Per the validated instructions of KOOS analysis, "as long as at least 50% of the subscale items are answered for each subscale, a mean score can be calculated. If more than 50% of the subscale items are omitted, the response is considered invalid and no subscale score should be calculated." In the event that the KOOS data is omitted, the participant will be regarded as a "drop out" and they will be included as such in the intent-to-treat analysis.

Subgroup analyses will be completed via 2-way ANOVA, stratified by FFMQ-15 and SF-12 scores. Subgroup analysis based on age, gender, comorbid behavioral health conditions, and duration of Knee OA symptoms may be considered.

Over-the-counter pharmacologic treatment of musculoskeletal pain is a common practice; given the near ubiquitous usage of these medications, this protocol does not preclude use of NSAIDs or acetaminophen. However, medication use will be monitored via weekly surveys and analyzed post-hoc as a potential confounder of the collected data.

Number of Subjects:

	# Planned to Enroll	# Enrolled	# Planned to Complete Study	TOTAL
Number of Subjects at Scott AFB	120	0	96	360
Number of Subjects at Travis AFB	120	0	96	
Number of Subjects at Nellis AFB	120	0	96	

**If any location recruits more subjects, they will be allowed to continue recruiting not to exceed the total number of subjects for all locations.*

7. STUDY DURATION

Duration of Study:

Approximate duration of the study: 3 years

8. LOCAL AND EXTERNAL SUPPORT SERVICES

Local and External Support Services: None

Describe the plan for training	☒Not applicable – no training of non-study personnel required

9. INTRAMURAL (GME) AND EXTRAMURAL FUNDING SUPPORT

Intramural (GME) and Extramural Funding Support:
A grant application was awarded in the amount of $25,000. Distribution of funds is pending IRB approval.

10. DRUGS, BIOLOGICS, DIETARY SUPPLEMENTS, AND MEDICAL DEVICES

Does the study plan dictate the use of any of the following?	
A drug	☒No
A biologic	☒No
A compound intended to affect structure or any function of the body	☒No
A dietary supplement or substance *generally recognized as safe* that will be used to diagnose, cure, mitigate, treat, or prevent disease	☒No
A medical device	☒No

Is this research an "applicable clinical trial" which must be registered on ClinicalTrials.gov?
☒No

Use of a placebo in place of standard therapy:		
Is a placebo being used in place of standard therapy?	☒No	☐Yes

11. MEDICAL RESEARCH AREA

☒Orthopedics	☒Family Medicine	☒Family Medicine Residency	

12. ATTACHMENTS

1. Form A, Signature Sheet
2. Form A-2, Study Personnel Listing
3. Form D, Informed Consent Document
4. H15 Template, HIPAA Authorization Document
5. Five Facet Mindfulness Questionnaire-15 (FFMQ-15) survey
6. Osteoarthritis Outcome Score (KOOS)
7. Short Form-12 (SF-12)
8. Study Diary
9. OA Informational Handout
10. OA Study Flyer
11. Screening Visit Med Hx Questionnaire
12. Telephone Eligibility Script
13. Rx3 Home Exercise Program
14. Week 12 survey
15. Weekly email script
16. Weekly survey