OA Clinic-Community CARE Model (*OA CARE*)

NCT Number: NCT05349500

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Protocol Number: 22-0865

NCT Number: NCT05349500

Principal Investigator: Kelli D. Allen, PhD

Sponsor: University of North Carolina at Chapel Hill

Grant Title: Optimizing Osteoarthritis Care through Clinical and Community Partnership

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Version Number: 4.0

Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale
8.1	Added language that the questionnaires at the 12-month follow-up visit may be done over the phone instead of in-person	Change made to reduce in-person visit time and participant burden

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Council on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812).

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form(s) must be obtained before any participant is consented. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form(s) will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

INVESTIGATOR'S SIGNATURE

The signature below constitutes the approval of this protocol and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

Principal Investigator or Clinical Site Investigator:

Signed: _____ Date: _____

Name:

Title:

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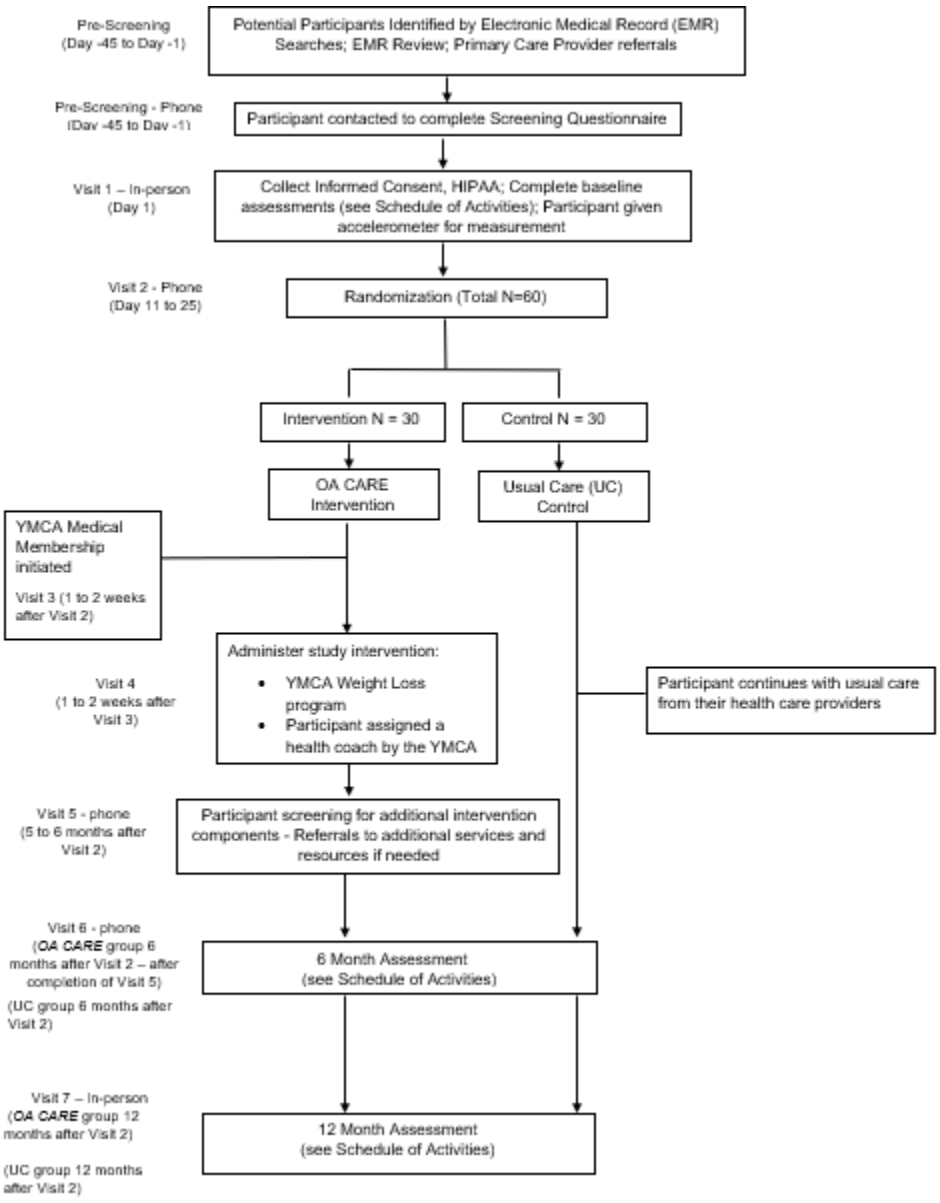
1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	**OA Clinic-Community CARE Model (*OA CARE*)**
Grant Number:	1 R21 AR080309-01
Study Description:	The overall objective of this study is to conduct a randomized pilot trial of *OA CARE* among n=60 patients with knee and/or hip osteoarthritis (OA) and overweight / obesity who are not currently meeting physical activity recommendations. Participants will be randomly assigned to *OA CARE* or a usual care (UC) group. Assessments will be conducted at baseline, 6 months and 12 months.
Objectives*:	**Specific Aim 1: Assess the feasibility and acceptability of *OA CARE*.** Feasibility metrics will include recruitment rate, completion rates for weight loss and exercise program visits, referrals to and utilization of services noted above and proportion of participants completing follow-up assessments. Acceptability of *OA CARE* will be evaluated from both patient and Primary Care Provider (PCP) perspectives. **Specific Aim 2: Obtain <u>preliminary</u> data on the efficacy of *OA CARE* with respect to the primary outcome of change in total Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score.** The WOMAC will be administered at baseline, 6-months and 12-months, along with secondary outcomes including body weight, physical activity, physical function, sleep measures and psychological measures. We will also collect preliminary data on costs of *OA CARE*.
Endpoints*:	Primary Endpoint: WOMAC Total Score. This will be assessed at baseline and 6-month and 12-month follow-up time points. Secondary Endpoints: Objectively assessed physical activity (PA), measured via accelerometer, body weight, and objective assessments of physical function; WOMAC self-reported pain and function. These will be assessed at baseline and 6-month and 12-month follow-up time points. Exploratory Endpoints: self-reported sleep and psychological measures, balance, and preliminary data on costs of *OA CARE* Feasibility and acceptability metrics include recruitment, retention, intervention delivery, and outcome assessment. Perceptions of acceptability will be obtained from patients and providers using open-ended questions.

Study Population:	N = 60 participants with knee and/or hip osteoarthritis (OA) and overweight / obesity who are not currently meeting physical activity recommendations. We will enroll both males and females from all racial and ethnic backgrounds.
Phase* or Stage:	Exploratory pilot trial
Description of Sites/Facilities Enrolling Participants:	We will recruit patients from UNC Health. In particular, we will partner with the UNC Internal Medicine Clinic and UNC Family Medicine.
Description of Study Intervention/Experimental Manipulation:	*OA CARE* includes evidence-based behavioral weight management and exercise interventions, as well as tailored referrals to physical therapy, psychological interventions, additional weight / nutrition-related services and sleep-related services based on patient-specific needs and in coordination with the PCP.
Study Duration*:	2 years
Participant Duration:	12 months

1.2 SCHEMA


Pre-Screening
(Day -45 to Day -1)
Potential Participants Identified by Electronic Medical Record (EMR) Searches; EMR Review; Primary Care Provider referrals
Pre-Screening - Phone
(Day -45 to Day -1)
Participant contacted to complete Screening Questionnaire
Visit 1 – In-person
(Day 1)
Collect Informed Consent, HIPAA; Complete baseline assessments (see Schedule of Activities); Participant given accelerometer for measurement
Visit 2 - Phone
(Day 11 to 25)
Randomization (Total N=60)
Intervention N = 30
Control N = 30
OA CARE Intervention
Usual Care (UC) Control
YMCA Medical Membership initiated
Visit 3 (1 to 2 weeks after Visit 2)
Visit 4
(1 to 2 weeks after Visit 3)
Administer study intervention:
YMCA Weight Loss program
Participant assigned a health coach by the YMCA
Participant continues with usual care from their health care providers
Visit 5 - phone
(5 to 6 months after Visit 2)
Participant screening for additional intervention components - Referrals to additional services and resources if needed
Visit 6 - phone
(OA CARE group 6 months after Visit 2 – after completion of Visit 5)
(UC group 6 months after Visit 2)
6 Month Assessment
(see Schedule of Activities)
Visit 7 – In-person
(OA CARE group 12 months after Visit 2)
(UC group 12 months after Visit 2)
12 Month Assessment
(see Schedule of Activities)

1.3 SCHEDULE OF ACTIVITIES

	Pre-screening (Pre-consent)	Visit 1 Day 1	Visit 2 Day 11 to 25	Visit 3 (1 to 2 weeks after Visit 2)	Visit 4 (1 to 2 weeks after Visit 3)	Visit 5 (5-6 months after Visit 2)	Visit 6 (OA CARE 6-Months after Visit 2; Usual Care 6-months after Visit 2)	Visit 7 (OA CARE 12-months after Visit 2; Usual Care 12-months after Visit 2)
EMR Review Eligibility	X							
Screening Phone Call	X							
Informed Consent & HIPAA		X						
Outcome Measures								
Objectively Assessed Physical Activity (accelerometer)		X					X	X
Patient Reported Measures:								
-Physical Function (WOMAC)		X					X	X
-Pain (WOMAC)		X					X	X
-Sleep (STOP Questionairre and Insomnia Severity Index)						X		
-Psychological Measures (Patient Health Questionnaire-8, Pain Catastrophizing Scale and Arthritis Self-Efficacy Scale)		X					X	X
-Modified version of the Community Health Activities Model Program for Seniors (CHAMPS) Physical Activity Measure		X					X	X
BMI measure							X	
Physical Performance Measures:								
-30-second stair stand test		X						X
-Timed up-and-go test		X						X
-2-minute march test		X						X
-Single Leg Stance Test		X						X
Participant Characteristics		X						
Acceptability								X
Randomization			X					
Control & Experimental Interventions:								
-*OA CARE*				X	X	X	X	X
-Usual Care Control							X	X
Adverse Event Reporting			X	X	X	X	X	X

2 INTRODUCTION

2.1 STUDY RATIONALE AND BACKGROUND

2.1.1. CLINICAL SIGNIFICANCE

Osteoarthritis (OA) is a Significant Burden for Individuals and Health Care Systems. OA affects over 32 million U.S. adults (1 in 7) and is a leading cause of pain and disability [1]. OA also has substantial impacts on work participation, mental health, sleep, development of other chronic conditions and even mortality [2]. Already associated with significant health care utilization and costs, the prevalence of OA is expected to rise substantially in coming decades [1]. This will place increasing demands on health care systems, highlighting the importance of developing and implementing efficient models that ensure a high quality of care for patients.

There are Persistent Deficiencies in Quality of Care for OA. Multiple studies have highlighted discordance between guideline-based OA care and actual clinical practice [3-7]. Despite agreement across OA treatment guidelines regarding the effectiveness and centrality of lifestyle (e.g., weight management, physical activity) and rehabilitation therapies [8], pass rates for quality indicators related to these therapies are only about 40% [4]. Data from primary care visits involving treatment for OA in the U.S. show that <50 out of 1000 addressed physical therapy as a potential treatment, and only about 250 out of 1000 addressed core lifestyle components [9]. Other studies have also documented low use of and recommendations for behavioral and rehabilitative therapies [3,5-7]. For example, in analyses of patients with knee OA across 3 different U.S. health systems, only 40-50% of patients had ever received physical therapy for this condition [5]. *These gaps in care are highly problematic, as they fail to engage patients with evidence-based treatments that are known to improve key outcomes including pain, disability, mental health and even disease progression* [10-13].

Evidence-Based Care Models are Needed to Improve OA Care Quality in the US. In response to the well-established deficiencies in care quality for knee and hip OA, there has been increasing interest in the development of systematic OA care models internationally[14-17]. Care models are defined as organized, planned approaches to improving health, focusing on particular patient populations (e.g., individuals with OA) to ensure that every patient receives optimal medical care [18]. Although there have been several randomized controlled trials (RCTs) of OA care models [14,15,19], there are three major limitations with respect to how this research can inform care for OA in the U.S. First, there have been no RCTs of OA care models in the U.S., and models developed in other countries are not designed to fit the organizational structures or payment models of U.S. healthcare systems. Second, the effectiveness of previously studied OA care models has been limited; we believe a key weakness has been the lack of robust incorporation of lifestyle components, particularly weight loss [15,19]. Third, prior models have been limited in terms of reach and sustainability because of significant requirements for busy health care providers [14,15,17,19]. *OA CARE will address each of these challenges, building an efficient, scalable model that is designed for sustainability and adequately addresses all components of guideline-concordant care.* This exploratory trial will accomplish key steps toward the first RCT of an OA care model in the U.S.

2.1.2. SCIENTIFIC RATIONALE

The *OA CARE* model incorporates the following 4 key principles and evidence from the scientific literature: 1) In alignment with OA treatment guidelines,[8,10,20] *OA CARE* takes a multifactorial approach that includes both pharmacological and non-pharmacological components. 2) *OA CARE* emphasizes delivery of lifestyle interventions, which are considered first-line treatments, appropriate for all patients with hip and knee OA [8,10,20]. 3) *OA CARE* involves a stepped care approach, in which patients begin with first-line interventions (weight management and physical activity) and then advance to additional therapies as needed.[21] A stepped care approach is efficient, patient-centered and supported by multiple studies, including our recent trial of a STepped Exercise Program for Knee Osteoarthritis (STEP-KOA).[21,22] 4) *OA CARE* will involve an innovative partnership with the YMCA to deliver weight management and exercise programs. The Centers for Disease Control and Prevention, Institute of Medicine and other organizations have recommended and prioritized clinic-community partnerships based on evidence for effectiveness [23]. These partnerships address the problems of limited time in clinical visits and the large number of patients who need these types of services.

2.1.3. PRIOR STUDIES AND RATIONALE FOR DEVELOPMENT

This study builds on our team's successful trials, programs and collaborations, including the following:

- We have collectively conducted over a dozen trials of behavioral interventions that support the evidence base for weight management, exercise, physical therapy, psychological and multi-component interventions as effective treatments for knee and hip OA [22,24-37]. These trials have given our team ample experience in patient recruitment, behavioral intervention delivery and fidelity monitoring, outcome assessment, and robust statistical analyses. We also have experience in delivering interventions involving PCPs and the use of algorithms to guide patient referrals to specific OA treatments [29,30].

- The Osteoarthritis Action Alliance (OAAA), a key partner (Dr. Callahan, Director), is a national coalition of over 130 organizations with a mission of reducing the public health burden of OA. The OAAA has experience in working with the YMCA (one of their member organizations) and other community organizations to deliver evidence-based lifestyle interventions, has developed stakeholder-informed patient and provider OA educational tools, and is engaged with vast network of partner organizations that will be instrumental in future implementation of *OA CARE*.

- *OA CARE* has been developed in partnership with key stakeholders. At the outset of developing this care model, we convened a group of clinicians and clinic administrators representing Internal Medicine, Family Medicine, Orthopedics, Physical Therapy and Rheumatology. *OA CARE* is based on this group's input regarding current gaps in care and processes that would be feasible and sustainable for clinics and providers. We also received input from on the project from our Thurston Arthritis Research Center Patient Stakeholder Advisory Board; they emphasized the importance of including rural patients and suggested that for patients who receive physical therapy during the study, we aim to integrate this with exercise opportunities at the YMCA, since this could enhance the benefits of physical therapy visits and augment integration of *OA CARE* components. We will engage with these stakeholder groups throughout all phases of this research program.

- The YMCA is currently engaged in clinic-community partnership efforts of direct relevance to this study. In particular, our local partners at the Triangle YMCA are currently funded by Blue Cross Blue Shield to conduct a 5-year project focused on referrals of patients from health systems to YMCA Medical Memberships, which include access to a variety of group programs plus health coaching. Their project aims to evaluate YMCA Medical Memberships as a population health approach and potential coverage as a health benefit; these goals are directly aligned with our plans for implementing and evaluating *OA CARE*. In addition, the Triangle YMCA has set up processes for sharing patients' outcome data with their PCPs through the electronic health record (EHR). The Triangle YMCA has been very successful during their first year of this project, enrolling >700 patients from 7 major health systems including University of North Carolina (UNC) Health.

2.2 RISK/BENEFIT ASSESSMENT

2.2.1 KNOWN POTENTIAL RISKS

Emotional distress: it is unlikely that the types of questions participants will be asked in this study will result in emotional distress, but we understand that participants may be uncomfortable with answering questions about some aspect of their health or other things about them. To minimize this risk, we will let participants

know they may choose not to answer any study questions and can still be involved in the study. Additionally, participants in the *OA CARE* intervention will have contact information for the study team (e.g. *OA CARE* Navigator) and a YMCA health coach to discuss any concerns.

Breach of confidentiality: we will be collecting some elements of personal health information necessary for the study. To minimize breaches of confidentiality, all data will be stored on a secure UNC server or a UNC IRB approved platform for sharing PHI (with YMCA) and paper information will be stored in locked filing cabinets in the office of a study team member, and only approved study personnel will have access to those data.

Personal health information (e.g. patient name and contact information only) will be shared with YMCA health coaches and personnel conducting the YMCA weight loss and exercise programs. Any information shared between approved UNC study team members and YMCA personnel will be done verbally by phone, by encrypted email or a UNC IRB approved platform for sharing PHI.

For participants in the *OA CARE* intervention, personal health information (e.g. patient name and DOB or MRN) will be shared with the participant's PCP, as part of the brief progress reports sent by the *OA CARE* Navigator . Any information shared between approved UNC study team members (e.g. *OA CARE* Navigator) and the participant's PCP will be done by encrypted email or UNC IRB approved platform for sharing PHI.

Risks of Exercise: Participants in the *OA CARE* intervention will be involved in physical activity programming at the YMCA. This will be tailored to individuals with knee OA. However, exercise programs may be associated with risk of injury, muscle soreness, and joint pain. The risk of sudden death during physical activity is about 1 death per 656,000 hours of physical activity. In general, the risk of these events with moderate physical activity is very low.

Risks of weight loss interventions: Participants in the *OA CARE* intervention will be involved in a weight management program at the YMCA. Side effects associated with weight loss in general may be hair loss, fatigue, weakness, gall bladder disease, and electrolyte abnormalities. Also, low blood sugar or low blood pressure (lightheaded or fainting) may occur during weight loss if a participant is taking medications for diabetes or high blood pressure. These risks are not specific to this research but also apply to usual care.

2.2.2 KNOWN POTENTIAL BENEFITS

Participants may experience improvements in pain, physical function or other symptoms related to OA, from participating in the OA Care program. It is possible that this study may not benefit participants directly, but participation in this study may lead to information that can benefit other patients with knee and/or hip OA, as well as their health care providers.

2.2.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

This is a minimal risk study with physical risks that are comparable to those that would be encountered with exercise programs in clinical or community settings. Furthermore, we do not anticipate any significant psychological, social, financial, or legal risks to be associated with participation in this study. Given the high and increasing rate of OA, the persistent deficits of physical inactivity, and the lack of a standard, evidence-based approach to address these deficits in primary care settings, we believe the value of the information to be gained outweighs the risks of participation in the study.

3 STUDY OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
Assess the feasibility and acceptability of *OA CARE*	Feasibility metrics will include recruitment rate, completion rates for weight loss and exercise program visits, referrals to and utilization of services noted above and proportion of participants completing follow-up assessments. Acceptability of *OA CARE* will be evaluated from both patient and PCP perspectives. PCP perspectives and recommendations will be conducted as a stakeholder engagement activity; PCPs will not be considered research participants.	These metrics are essential for assessing the feasibility of conducting a larger scale trial of *OA CARE*.
Obtain <u>preliminary</u> data on the efficacy of *OA CARE* with respect to the primary outcome of change in total Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score.	Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain, stiffness, and function subscales, assessed at baseline, 6 months and 12 months. We will separately examine WOMAC pain and function subscales as secondary outcomes.	This primary metric will be assessed because it is a key outcome in OA and can be improved with regular PA. The 12-month time point corresponds to the end of the *OA CARE* intervention, and the 6-month time point will allow assessment of the time course of changes in outcomes.
Secondary		
Obtain data on the efficacy of the *OA CARE* program with respect to improvement in body weight, physical activity and physical function.	Physical activity will be accessed via accelerometer. Moderate to vigorous physical activity (MVPA; primary metric), light intensity activity, sedentary minutes, step counts and other PA metrics, assessed at baseline, 6 months and 12 months. Physical Function tests: 30-second chair stand test, timed up-and-go test, 2-minute march test and single	These secondary metrics will be assessed because they are also key outcomes in OA, and they map onto the different components of the *OA CARE* intervention. The 12-month time point corresponds to the end of the *OA-CARE* intervention, and the 6-month time point will allow assessment of the time courses of changes in outcomes.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
	leg stance assessed at baseline and 12 months. Body Weight will be assessed using a research / clinical grade scale. Participants' height will also be measured to calculate body mass index (BMI).	
Tertiary / Exploratory		
Obtain data on the efficacy of the *OA CARE* program with respect to the change in exploratory outcomes.	Exploratory outcomes include psychological measures (Patient Health Questionnaire-8, Pain Catastrophizing Scale and Arthritis Self-Efficacy Scale) assessed at baseline, 6 months and 12 months. We will collect self-reported sleep measures (STOP Questionnaire and Insomnia Severity Index) for the *OA CARE* intervention. We will also collect preliminary data on costs of *OA CARE*.	These outcomes are also important for patients with knee OA and map onto *OA CARE* intervention components. The 12-month time point corresponds to the end of the *OA-CARE* intervention, and the 6-month time point will allow assessment of the time courses of changes in outcomes.

4 STUDY DESIGN

4.1 OVERALL DESIGN

The aim of this study is to conduct an exploratory randomized controlled trial with 60 patients with knee and / or hip OA equally randomized to *OA CARE* or a usual care (UC) control group (Figure 1) . Sub-aims are as follows:

Aim 1. Assess the feasibility and acceptability of *OA CARE*. Feasibility metrics will include recruitment rate, completion rates for weight loss and exercise program visits, referrals to and utilization of services noted above and proportion of participants completing follow-up assessments. Acceptability of *OA CARE* will be evaluated from both patient and PCP perspectives.

Aim 2. Obtain preliminary data on the efficacy of *OA CARE* with respect to the primary outcome of change in total Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score. The WOMAC will be administered at baseline, 6-months and 12-months, along with secondary outcomes including body weight, physical activity, physical function (baseline and 12 months only), sleep measures and psychological measures. We will also collect preliminary data on costs of *OA CARE*.

This will be an exploratory RCT with 60 patients equally randomized to *OA CARE* or a usual care (UC) control group (Figure 1); randomization will be in block sizes of 20. Assessments will occur at baseline, 6-month follow-up and 12-month follow-up. The UC group will be offered a 12-month YMCA Medical Membership (described below) once they have completed follow-up assessments.

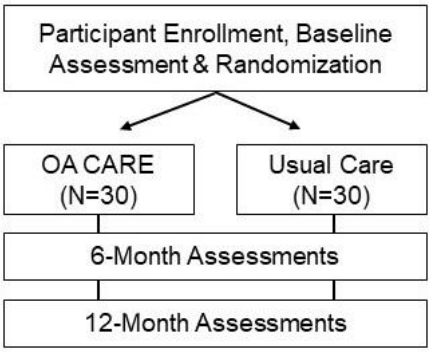


Figure 1. Study Design

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Although this exploratory trial is not designed with statistical power to test the efficacy of *OA CARE*, we have included a UC group (rather than conducting a single-group study) for several reasons. First, this provides an opportunity to assess acceptability of randomization to a UC group, from the patient perspective. Second, we will be able to evaluate follow-up rates for both groups, which will inform potential adaptations and sample size estimation for a larger trial. Third, this will provide a better preliminary assessment of the efficacy of *OA CARE* (Aim 2) than a single group pre-post trial, since improvement is consistently observed in control groups within OA trials [22,29,31,38]. We have specifically selected a UC control group (versus an attention control condition) because our ultimate goal is to test how well *OA CARE* performs relative to the typical care patients receive for OA. Assessments for this trial will be conducted at baseline, 6-months (corresponding to the beginning of the second phase of *OA CARE*), and 12-months (intervention completion).

4.3 JUSTIFICATION FOR INTERVENTION

This research addresses a clear need to improve care for patients with OA through an evidence-based, comprehensive and sustainable care model. This project lays the groundwork for an implementation-focused RCT that will collect rigorous cost data to inform payment models. Involvement of key stakeholders, as well as integration with national organizations including the YMCA and OAAA, will lead to a generalizable approach and strategies for widespread implementation in U.S. healthcare systems.

4.4 END-OF-STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed 12-month follow-up assessment.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

Participants for this trial will be patients with a clinician diagnosis of knee or hip OA, self-reported knee or hip pain of ≥3 (scale of 0-10) on most days of the week, body mass index (BMI) ≥27 $kgm^{2,}$, and not currently meeting physical activity recommendations [39]. We will base study inclusion on a clinician diagnosis of hip or

knee OA, rather than obtaining new radiographs, because *OA CARE* is designed for providers to initiate at any point in the course of care (not necessarily directly following a diagnosis or new imaging). The rationale for BMI and physical activity criteria is that patients with higher BMI and who are inactive are at greater risk for OA progression and worse outcomes, and weight management and exercise are key components of *OA CARE* [42,43]. We chose a minimum BMI of 27 kgm^2 because of the association with earlier mortality and the precedence of this threshold in other OA trials [11,32,44].

5.2 EXCLUSION CRITERIA

Exclusion Criteria and Sources of Information		
Criterion	EMR	Phone Screening
No internet access and a device (computer, tablet, smartphone) to access the virtual weight loss intervention		X
Pain in chest when performing physical activity		X
Pain in chest when not performing physical activity		X
No documented diagnosis of knee or hip OA	X	X
No lower extremity surgery in the past 6 months	X	X
Significant cognitive impairment	X	X
Psychosis	X	X
Uncontrolled Substance abuse disorder	X	X
Severe hearing or visual impairment	X	X
Serious/terminal illness as indicated by referral to hospice or palliative care	X	X
Hospitalization for cardiovascular event in last 6 months	X	X
History of ventricular tachycardia	X	X
Unstable chronic obstructive pulmonary disease (2 hospitalizations within the previous 6 months and/or on oxygen)	X	X
Stroke with moderate to severe aphasia	X	X
Recent history (last 6 months) of three or more falls		X
Planning total joint replacement in next 6 months		X
Any other health conditions determined by the study team to be contraindications to a home exercise program or weight loss.	X	X
Current participation in other study related to knee or hip osteoarthritis, weight loss or physical activity		X
Unable to speak English	X	X
Pregnant or planning to become pregnant	X	X

5.3 LIFESTYLE CONSIDERATIONS

N/A

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in this study but are not subsequently assigned to the study intervention or entered in the study. Individuals who do not meet the criteria for participation in this trial (screen failure) because of meeting one or more exclusion criteria (e.g., development of an exclusionary health condition) will not be rescreened.

5.5. STRATEGIES FOR RECRUITMENT AND RETENTION

We will recruit patients from UNC Health. In particular, we will partner with the UNC Internal Medicine Clinic and UNC Family Medicine, which serves high proportions of patients who are African American and non-white Hispanic, as well as uninsured patients. This is important because of disparities in OA among these demographic groups[45], and our aim for *OA CARE* to particularly reach the most vulnerable patients. Our team has a strong track record of recruiting African American and non-White Hispanic patients [28,31,46]. Our main recruitment method will mirror the process by which we envision *OA CARE* will ultimately function in clinical settings. Specifically, PCPs will be asked to refer patients to *OA CARE*. This may occur via the EHR or another UNC approved method of transferring PHI. A study team member will then screen the EHR for potential exclusion criteria and contact the patient to assess interest and administer a brief screening questionnaire. If needed, we will also identify potential participants via an EHR data pull, then send introductory letters and follow up with a screening phone call. However, a key goal for this exploratory study is to develop procedures to maximize provider referrals, as this will be critical for downstream implementation. All eligible patients will be asked to attend a baseline visit that will involve completion of consent, baseline assessments and receipt of an accelerometer. Following return of the accelerometer, participants will be informed of their randomization assignment via telephone. A participant will be considered enrolled once they have consented and been randomized.

To facilitate completion of recruitment calls, as well as baseline and follow-up assessment calls, we will call participants on different times of day and different days, across multiple weeks. We have used this strategy successfully in prior studies to reach participants at times convenient to them.

6.0 STUDY INTERVENTIONS

6.1 STUDY INTERVENTION ADMINISTRATION

OA CARE Intervention

Overview. For patients, *OA CARE* includes evidence-based behavioral weight management and exercise interventions, as well as tailored referrals to physical therapy, psychological interventions, additional weight / nutrition-related services and sleep-related services based on patient-specific needs and in coordination with the PCP (Figure 2). These referrals will be based on screening questions administered six months after initiating weight management and exercise interventions; the rationale for this timing is that it allows us to evaluate which additional services patients may need after engaging in "first line" therapies for a meaningful period of time [4,8,10]. PCPs of patients enrolled in *OA CARE* will be given a video-based summary of ACR treatment guidelines [10], collaborate on patient referrals, and receive brief progress reports on their enrolled patients. An *OA CARE* Navigator will facilitate all activities within the care pathway, including scheduling patients for weight management and exercise classes (in collaboration with the YMCA), conducting 6-month screening questions, coordinating referrals with PCPs, preparing patient progress reports for PCPs, and serving as a point person for both patient and PCPs. Importantly for implementation, the *OA CARE* Navigator role does not require clinical or other specialized expertise, so in clinical settings this role could be performed by a variety of personnel (e.g., chronic care managers, nurses, schedulers).

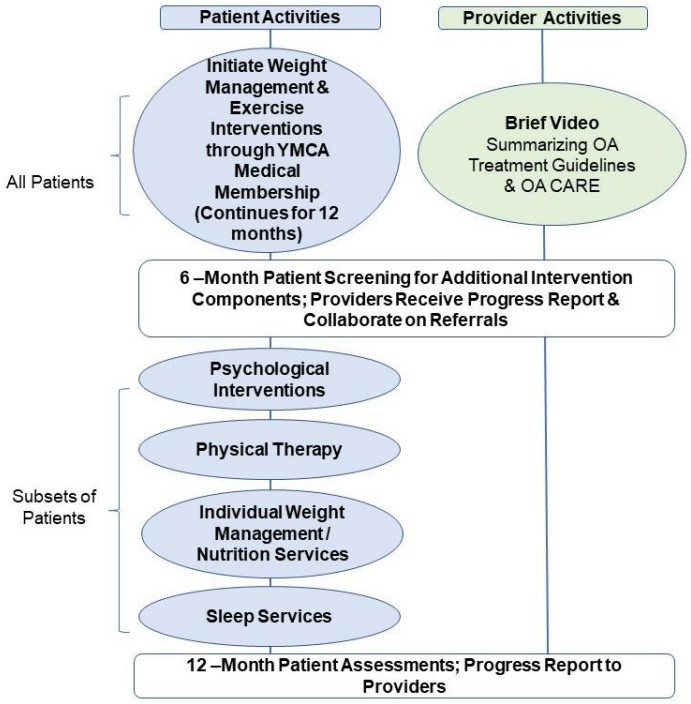


Figure 2. OA CARE Intervention

Weight Loss & Exercise Interventions. Evidence-based weight loss and exercise programs will be delivered by the Triangle YMCA, within the structure of the Medical Membership. (All services provided to study participants by the YMCA will be their standard programming; they will note be delivering a study-specific intervention.) This membership provides access to multiple group exercise programs, exercise facilities, and a health coach who assists members with meeting health goals and selecting appropriate programs and classes. All patients in *OA CARE* will begin with participation in the YMCA's Weight Loss Program (Program). This program involves 12 weekly sessions that include goal-setting, food and activity tracking, introduction to physical activity offerings, and weigh-ins. This Program is based on best practices from evidence-based behavioral weight loss programs. Participants may repeat the program following the first 12-week session if they have not met weight loss goals and / or would like continued structure and support for these behavior changes. The Triangle YMCA will deliver the Weight Loss Program to *OA CARE* members in groups of approximately 10; this will provide cohesion for *OA CARE* participants. In the beginning of the study, the Program will be delivered virtually (e.g. video conferencing platform) for feasibility reasons (e.g., potential for study participants to reside in different geographic locations that would make travel to a central location challenging). However, the Program may be offered in-person in the future. During the screening call, we will assess whether the patient has internet access and a device (computer, tablet, smartphone) on which they can access the Program. If the patient screens ineligible for this reason, we will ask the patient if they would like to be contacted, if the Program is offered in-person at a future date. If we do offer the Program in person, this will no longer be considered an exclusion criterion. The YMCA offers many exercise programs and classes appropriate for individuals with OA. A YMCA health coach will assist participants with selecting an exercise program (including appropriateness based on their pain and functional limitations) and continuing to engage with exercise-based therapies throughout their 12-month involvement in *OA CARE.* The UNC study team will also give participants instructions regarding how to access a free Walk With Ease workbook (through the OAAA's online portal) and take advantage of other tools available through this program.

Additional Tailored Services. After 6-months, we will administer a series of questionnaires to assess patients' needs for and interest in additional interventions included in OA treatment guidelines (Table 1) [10,20]. Our multidisciplinary study team, which includes individuals with deep expertise in OA treatment and guidelines, has developed algorithms to guide these referrals. Patients will be given information on the types of interventions shown in Table 1 (via mail or email), and the *OA CARE* Navigator will engage patients in a shared decision-making process (via phone) regarding additional referrals, with a focus on interventions for which they meet criteria shown in Table 1. However, the *OA CARE* Navigator will facilitate referrals and recommendations for any services of interest to patients, regardless of criteria shown in the table. Any referrals for clinically-based services (e.g., physical therapy, sleep testing) will be coordinated with the PCP. Table 1 also shows examples of interventions and resources within each category, ranging from free, publicly available programs to individual clinical services; some services will be relevant regardless of geographic location and some will be customized based on local resources, as we have done previously [33]. The *OA CARE* Navigator will also call participants about a month later to follow up on any questions they may have regarding resources or referrals. The *OA CARE* Navigator may also conduct additional calls with a participant if needed to coordinate connection with resources or referrals.

Table 1. Criteria and Examples of Additional Tailored Services

Type of Service	Criteria	Example Interventions & Resources
Psychological Interventions	Subgroups for Targeted Treatment (STarT Back) Tool [47-49]: 4 or more psychosocial risk factors (pain bothersomeness, fear, worry, catastrophizing, depression) [50]	Free, evidence-based pain coping skills training programs (e.g. painTRAINER) and referral to local mental health providers who specialize in pain management
Physical Therapy	Persistent self-reported difficulty with walking or stair-climbing, balance difficulties, recent falls or pain as a limitation to engaging in regular exercise	Referrals based on based on patients' preferences for location, geography, and health insurance coverage
Weight Management & Nutrition Services	< 5% weight loss[51]	Referrals to registered dieticians and other credentialled clinicians who specialize in weight loss support
Sleep Services	Sleep apnea: "high risk" based on the STOP questionnaire, score ≥ 2 [52]. Insomnia: score ≥11 on the Insomnia Severity Index [53].	Referrals for sleep testing, recommendations for free, evidence-based cognitive behavioral therapy for insomnia programs (e.g., CBTI-Coach app), and referrals to local providers or group programs focusing on sleep-related therapies.

Provider Intervention. As noted above, we have intentionally designed the PCP intervention to be brief, therefore maximizing feasibility and engagement. There are three components to the PCP intervention. The first is a set of brief videos summarizing current OA treatment guidelines, with a focus on practical application and the role of the PCP. Second, providers will receive progress reports for their enrolled patients through encrypted email or other UNC approved method of sharing PHI; this will include changes in symptoms and health behaviors from the study team at 6- and 12-months. Third, providers will be involved with referrals to additional clinical services, as described above. The *OA CARE* Navigator will provide the PCP with information on patient requests for referrals, based on the 6-month assessment, and the referral process will follow the usual procedures within the primary care clinic.

6.2 FIDELITY

Interventionist Training

OA Care Navigator: The *OA Care* will be trained by the principal investigator prior to delivering the intervention. This training will include general instruction in intervention delivery steps, processes for communicating with YMCA personnel and PCPs vis email and the electronic health records, content for notes to PCPs, administration of 6-month screening questionnaires, and discussion of potential services and referrals during the 6-month phone call. For the 6-month screening questionnaires and discussion of referrals, training will

include mock sessions with both experienced study team members and non-study member volunteers (observed by the principal investigator). The *OA Care* Navigator will also view the video created for PCPs, as well as other materials from the OAAA, to become highly familiar with OA symptoms and care.

Fidelity Monitoring
Monitoring of Intervention Contacts. Dr. Allen or another experienced study team member will monitor study intervention contacts and provide feedback to the interventionists, including the following:

- *OA CARE* Navigator 6-month phone calls: The first 5 calls will be monitored with potential for additional calls if deemed appropriate by the principal investigator or other study team member. Monitoring will involve checks to ensure that all questions are asked per protocol, services and referrals are appropriately explained to patients, and the Navigator engages the patient in a meaningful discussion regarding their interest in services and referrals.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

The randomization scheme will be generated by the study statistician and stored within the study database. The database will be configured so that blinded study personnel (e.g., those conducting follow-up assessments) will not have access to randomization information. The participants will not be notified of randomization assignment until all baseline assessments are complete. In addition, an individual participant's randomization assignment will not be known to any study personnel until baseline assessments are complete.

6.4 STUDY INTERVENTION ADHERENCE

The study database will be used to track participants' completion of all assessment visits, as well as all contacts with the *OA CARE* Navigator. The coordinator will also maintain close communication with the *OA CARE* Navigator regarding facilitation of all activities within the care pathway. The YMCA will provide documentation of patients' participation in specific YMCA programs to the *OA CARE* Navigator; this information will also be summarized for PCPs. Also, for each patient, the *OA CARE* Navigator will maintain a checklist of intervention activities, target dates, dates of completion, and comments.

6.5 CONCOMITANT THERAPY

Participants will be permitted to continue any other OA treatment during the course of the study.

7 STUDY INTERVENTION/ DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

When a participant discontinues the *OA CARE* intervention, they will be asked if they are willing to continue with other remaining activities (e.g., follow-up assessments) based on the study protocol. If a clinically significant finding is identified after enrollment (e.g. health-related changes that may change the safety level of participation), the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE). The data to be collected at the time of study intervention discontinuation will include the reason(s) for discontinuing the participant from the intervention, and methods for determining the need to discontinue.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.
An investigator may discontinue a participant from the study for the following reasons:

- Lost-to-follow up; unable to contact subject
- Any event or medical condition or situation occurs such that continued collection of follow-up study data would not be in the best interest of the participant or might require an additional treatment that would confound the interpretation of the study
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

The reason for participant discontinuation or withdrawal from the study will be recorded in the study database. Participants who discontinue or are withdrawn will be replaced up to the point of randomization assignment being given to the participant. Once participants are given their randomization assignment, they will be counted toward the total study sample size and not replaced.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for the final, 12-month follow-up assessment. If a participant misses intervention calls or follow-up assessments prior to the 12-month time point and cannot be contacted during the time frame, the study team will still attempt to contact the participant for remaining calls / assessments. The study team must attempt to contact a participant at least 3 times, on different days of the week, different times of day, and across at least 2 weeks, before they are considered to have missed a visit / assessment or be lost to follow-up. These contact attempts will be documented in the study database.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 ENDPOINT AND OTHER NON-SAFETY ASSESSMENTS

Measures will be collected at baseline, 6-months and 12-months by a trained study team member blinded to randomization assignment. Measures will be administered in-person at baseline and 12-months and at 6-months via phone. We may schedule a time to call the participant before or after the in-person 12-month visit to complete the questionnaires over the phone. Participants will be paid $60 for baseline and 12-month assessments ($45 for in-person visits + $15 to wear and return the accelerometer) and $40 for 6-month assessments ($25 for phone-based assessments + $15 to wear and return the accelerometer).

Feasibility Metrics. We will compute the proportion of patients who are eligible and who consent to participate in the study, mean number of intervention visits attended, and proportion of participants who complete follow-up assessments. We will also determine the proportions of participants who meet criteria for and are interested in each type of additional intervention (at 6-month follow-up), and we will track participants' use of these services during the study period.

Acceptability of *OA CARE*. We will ask all participants in the *OA CARE* group to complete a series of satisfaction ratings and open-ended questions regarding different components of the intervention. We will not collect formal measures from referring PCPs. However, following the completion of the study, we will contact providers and ask for their suggestions on ways in which *OA CARE* could be improved. This will be approached as a stakeholder engagement type of activity, and PCPs will not be considered research participants for this purpose.

Primary Patient Outcome: Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). The primary outcome for this study is the WOMAC, a measure of lower extremity pain (5 items), stiffness (2 items), and function (17 items). All items are rated on a Likert scale of 0 (no symptoms) to 4 (extreme symptoms). The

WOMAC has well established psychometric properties including reliability, construct validity and internal consistency [54]. The WOMAC has been widely used in trials of behavioral interventions for patients with lower extremity OA, confirming its sensitivity to change in this context. In addition to the total WOMAC score (primary outcome), we will separately examine WOMAC pain and function subscales.

Secondary Patient Outcomes.

Body Weight. We will assess body weight using a research / clinical grade scale (e.g., Tanita) that will be calibrated regularly. We will also measure participants' height in order to calculate body mass index.

Physical Activity. All participants will be asked to wear an Actigraph GT3X+ (Pensacola, FL) [55]at the hip during waking hours for 7 days. We will use data processing and logistical methods we have used successfully in prior work [33]. Physical activity metrics will include minutes of any intensity activity (primary), minutes of moderate to vigorous intensity physical activity, step counts and sedentary time. We will also ask participants to complete a modified version of the Community Health Activities Model Program for Seniors Physical Activity Measure [56], which provides information on the types of activities in which participants are engaging.

Physical Function. We will administer tests recommended by the Osteoarthritis Research Society International for clinical trials of knee OA including a 30-second chair stand test and timed up-and-go test [57]. We will also include a 2-minute march test as an assessment of endurance [58] These tests will be conducted in accordance with established protocols [57,58].

Exploratory Patient Outcomes.

Sleep Measures. Sleep apnea symptoms will be assessed with the STOP Questionnaire [52], and insomnia symptoms will be assessed with the Insomnia Severity Index [53]. These measures were selected based on clinical practice guidelines [59].

Psychological Measures. We will assess depressive symptoms via the Patient Health Questionnaire-8 (8-item measure, higher [60], the Pain Catastrophizing Scale [61], and the Arthritis Self-Efficacy Scale [62,63]. These are all validated scales used widely in the context of OA trials.

Balance. We will assess balance with a single leg stance test, using established protocols [58]. The maximum possible standing time will be 30 seconds, and we will also designate whether participants achieve a commonly utilized threshold of 10 seconds.

Participant Characteristics. We will collect the following information to characterize the study sample: age, race / ethnicity, sex, education level, work status, household income, health insurance status, marital status, comorbid illnesses [64], joints with arthritis symptoms, and duration of knee / hip OA symptoms.

Costs. Although costs are not a primary focus of this exploratory trial, we will collect these data to refine processes for the larger trial. This will include costs of the YMCA Medical Membership, costs (to both the health system and patients) associated with additional clinical services that result from 6-month screening and referrals, and patients' self-reported costs for engaging any additional community-based services or programs.

8.2 SAFETY ASSESSMENTS

If a study team member learns of any adverse events (AEs) that occur in the course of participants' home exercise, this will be documented on the Adverse Events form, as described below.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS

This protocol uses the definition of adverse event from DHHS Office for Human Research Protections (OHRP): Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the

research (modified from the definition of adverse events in the 1996 International Conference on Harmonization E-6 Guidelines for Good Clinical Practice).

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS

This protocol uses the definition of serious adverse event from DHHS OHRP: any adverse event that results in death; is life-threatening (places the subject at immediate risk of death from the event as it occurred); results in inpatient hospitalization or prolongation of existing hospitalization; results in a persistent or significant disability/incapacity; results in a congenital anomaly/birth defect; or based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

All AEs will be assessed by the PI or co-investigators, if the PI is not available. The following guidelines will be used to describe severity:

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".]

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

All AEs will have their relationship to study procedures, including the intervention, assessed by the PI or co-investigators based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- Definitely Related – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- Probably Related – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- Not Related – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.3.3.3 EXPECTEDNESS

The PI or Dr. Saint-Surin (co-investigator on the study) will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study procedures.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an AE or serious adverse event (SAE) may come to the attention of study team members during study visits. All AEs, not otherwise precluded per the protocol, will be captured on the Adverse Event Form. Information to be collected includes event description, time of onset, PI or co-investigator's assessment of severity, relationship to study procedures (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study will be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical or psychiatric condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. Documentation of onset and duration of each episode will be maintained for AEs characterized as intermittent.

The Project Coordinator will record events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. Participants are identified in the EMR as a study participant and for each AE/SAE occurrence, research team members will receive an alert through EMR. AEs or SAEs may also be reported to study physical therapist during the course of intervention visits. Events will be followed for outcome information until resolution or stabilization.

8.3.5 ADVERSE EVENT REPORTING

Once Dr. Allen (or a co-investigator) is contacted about the adverse event, she / he will make a determination about the reporting requirements in accordance with UNC IRB guidelines.

The PI or a co-investigator will report any AEs to the UNC IRB that suggest new or increased risk to participants or others within 7 calendar days of when the PI became aware of the information. New or increased risk is defined as any incident, experience, outcome, or new information that are (1)unexpected, (2) related or at least possible related to participation in the research, and (3) indicates that subjects or others are at a greater risk of harm (including physical, psychological, economic, legal, or social harm)
For AEs that are not related to participation in the research and do not suggest new or increased risks to the participant, these will be reported to NIAMS on the bi-annual safety report submitted to the SO

8.3.6 SERIOUS ADVERSE EVENT REPORTING

Once Dr. Allen (or a co-investigator) is contacted about a serious adverse event, she / he will make a determination about the reporting requirements in accordance with UNC IRB guidelines. This will include notification of the UNC IRB within 24-hours if a study-related death and within 48 hours if another SAE.

All SAEs will be reported to the NIAMS (through the NIAMS Executive Secretary) within 48 hours of the investigator becoming aware of the event. The SAE Report Form will be completed and the SO's review of the SAE report will be shared with the NIAMS once received.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

N/A

8.3.8 EVENTS OF SPECIAL INTEREST

N/A

8.3.9 REPORTING OF PREGNANCY

N/A

8.4. UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS

This protocol uses the definition of Unanticipated Problems as defined by the Office for Human Research Protections (OHRP). OHRP considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets all of the following criteria:

(1) Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;

(2) Related or possibly related to participation in the research. *Possibly related* means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

(3) Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

OHRP recognizes that it may be difficult to determine whether a particular incident, experience, or outcome is unexpected and whether it is related or possibly related to participation in the research. OHRP notes that an incident, experience, or outcome that meets the three criteria above generally will warrant consideration of substantive changes in the research protocol or informed consent process/document or other corrective actions in order to protect the safety, welfare, or rights of participants or others.

The following corrective actions or substantive changes that could be considered in response to an unanticipated problem include:

- Changes to the research protocol initiated by the investigator prior to obtaining IRB approval to eliminate apparent immediate hazards to subjects;
- modification of inclusion or exclusion criteria to mitigate the newly identified risks;
- implementation of additional procedures for monitoring subjects; suspension of enrollment of new subjects;
- suspension of research procedures in currently enrolled subjects;

- modification of informed consent documents to include a description of newly recognized risks;
- provision of additional information about newly recognized risks to previously enrolled subjects.

Only a small subset of adverse events occurring in human subjects participating in research will meet these three criteria for an unanticipated problem. Furthermore, there are other types of incidents, experiences, and outcomes that occur during the conduct of human subjects research that represent unanticipated problems but are not considered adverse events. For example, some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place subjects or others at increased risk of harm, but no harm occurs.

8.4.2 UNANTICIPATED PROBLEMS REPORTING

All UPs will be reported to UNC IRB within 48 hours of the PI becoming aware of the event. All UPs will be reported to the NIAMS and the SO (through the NIAMS Executive Secretary) within 48 hours of the PI becoming aware of the event.

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Participants will be given any new information gained during the course of the study that might affect their willingness to continue participation in the study.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

The aim of this study is to conduct an exploratory randomized controlled trial with 60 patients with knee and / or hip OA equally randomized to *OA CARE* or a usual care (UC) control group. Sub-aims and associated hypotheses are:

Aim 1. Assess the feasibility and acceptability of *OA CARE*. There are no specific hypotheses associated with this aim. Analyses will be descriptive in nature.

Aim 2. Obtain <u>preliminary</u> data on the efficacy of *OA CARE* with respect to the primary outcome of change in total Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score. We hypothesize that participants in OA CARE will have clinically meaningful improvements in WOMAC scores at 6- and 12-month follow-up relative to a UC control group. Similarly, we hypothesize that participants in OA CARE will have greater improvements in secondary and exploratory outcomes compared with the control group.

9.2 SAMPLE SIZE DETERMINATION

Due to the exploratory nature of this trial, the objective is to inform estimates for a larger RCT. Accordingly, we do not necessarily expect this trial to be highly powered. However, we do note that for the projected total of n=60 enrolled participants, equally allocated between the two arms of the trial at the two-sided 0.05 significance level, and accounting for a conservative effect of clustering within the *OA CARE* arm, we would exceed 80% power to detect an effect size of at least 1.7 *SD*. This choice of sample size is deemed to be feasible for completion within the time frame of this exploratory trial and will allow sufficient experience with intervention delivery to inform the larger trial. We expect some drop-out and loss-to-follow-up among participants, and this exploratory trial will contribute to our sample size estimation for the larger RCT in this regard. However, based on rates of drop-out in prior trials [28,29,31], our target sample size of 60 participants will allow ample experience with study procedures. Our analytic strategy (described below) will also accommodate missing data due to dropout, missed visits, and loss-to-follow-up.

9.3 POPULATIONS FOR ANALYSES

The primary analyses will be conducted using an intent-to-treat approach. Supportive exploratory analyses may be conducted to consider samples with greater completion of study intervention visits. Since this is an exploratory trial, the nature of these supportive analyses will be based on observed patterns of intervention contacts.

9.4 STATISTICAL ANALYSES PLAN

The primary patient outcome of the total WOMAC score will be statistically analyzed between experimental groups across the follow-up time points through a general linear mixed model (GLMM). Fixed effects will include indicators for the *OA CARE* group, the 12-month follow-up time point, and their interaction (group by time). Additional fixed effects will be baseline total WOMAC score and possibly any covariates exhibiting random imbalance between groups. Random effects will be included for patients (to account for their repeated measures) and for grouping within the *OA CARE* arm (e.g. 10-participant Weight Management Program groups) to account for clustering. Customized statistical linear contrasts will be constructed to estimate the effect size via the difference in means for *OA CARE* versus usual care, along with the corresponding 95% confidence limits, separately at 6- and 12- months, to provide useful estimates that will inform the sample size estimation for the subsequent trial. Estimated correlations among the follow-up time points, as well as estimated within-cluster intraclass correlation for the *OA CARE* arm, will also be useful in this regard. Exploratory testing of efficacy will also be conducted using these statistical contrasts. The approach outlined above will be repeated separately for the WOMAC pain and function subscale scores, as well as for the secondary outcomes identified above. If any of these outcomes exhibit distributions that deviate markedly from normality, alternatives will include transformations to normalize the distribution and variable categorization with appropriate data analysis (e.g., mixed-effects logistic models or logistic models utilizing generalized estimating equations to accommodate correlated observations). An intent-to-treat approach will be followed in these analyses to provide a conservative approach. A two-sided 0.05 significance level will be applied to each outcome with no adjustment for multiple comparison in keeping with the exploratory nature of the trial. The GLMM approach utilizes all available follow-up data and accommodates missing data under a missing at random (MAR) paradigm. If missing data are extensive and deemed not to be MAR, analyses will be conducted using multiple imputation, yielding complete data for all participants. The feasibility and acceptability metrics will be summarized through descriptive statistics, along with corresponding 95% confidence intervals, separately by experimental arm when appropriate. This includes frequencies and proportions of patients who are eligible, who consent to participate in the study, who complete follow-up assessments, who meet criteria for and are interested in each type of additional intervention (at 6-month follow-up), and who use of these services during the study period. Means and standard deviations will be computed for the number of intervention visits attended by participants.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks will be given to the participant and written documentation of informed consent will be completed prior to starting the study intervention. The following consent materials are submitted with this protocol: Adult Consent Form.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Once a potential participant meets the medical record and telephone screening criteria for eligibility, and is interested in participating, they will be asked to attend a baseline visit that will involve completion of consent, baseline assessments and receipt of an accelerometer. No other study activities will occur until this process is completed.

We will use a UNC IRB approved consent form / script with included language that satisfies the HIPAA requirements and outlines the protection of health information utilized in the study.

Written informed consent will be obtained by a trained study team member. The study team member will read the IRB approved consent form to the potential participant and provide an opportunity for him/her to ask any questions that they may have about the research study. We anticipate this process to take approximately 20 minutes, but this time will not be limited should a participant have additional questions or concerns regarding the study. During this phase of the consent process, it will be stressed that the participant is not obligated to participate in the study, that participation is completely voluntary, and that he/she may withdrawal from the study at any time without penalty. Also, potential risks from participating in the study will be outlined in the consent form, as are the measures taken to protect against study specific risks. Once the information in the consent form is fully reviewed and understood by the individual, he/she will be asked to decide at that time if they would like to voluntarily participate in the research study. If the individual does choose to participate in the study, both the study team member and the participant will sign two copies of the informed consent form. The participant will receive one copy for their records and the other copy will be stored in a locked file cabinet of a study team member.

If after review of the consent form, the potential participant is not sure they would like to participate in the study at this time, they may choose to consider the study further, and then contact the study team if they decide later that they would like to participate.

Once informed consent has been collected, the study team member will collect written HIPAA authorization, and no activities will commence until this is received by the study team.

Participants will only be included if they have capacity to give legally effective consent. Additionally, this study will only recruit participants whom are English speakers.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, funding agency, and regulatory authorities. If the study is prematurely terminated or suspended, the PI will promptly inform study participants, the IRB, and sponsor/funding agency and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met

- Determination of futility

The study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the funding agency, sponsor, IRB or other relevant regulatory or oversight bodies (OHRP, SO).

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, the safety and oversight monitor(s), and the sponsor(s) and funding agency. This confidentiality is extended to the data being collected as part of this study. Data that could be used to identify a specific study participant will be held in strict confidence within the research team. No personally-identifiable information from the study will be released to any unauthorized third party without prior written approval of the sponsor/funding agency.

Personal health information (e.g. patient name and contact information) will be shared with YMCA so they may contact participants to enroll in the medical membership and participate in programs. Any information shared between approved UNC study team members and YMCA personnel will be done verbally by phone, by encrypted email or a UNC IRB approved platform for sharing PHI.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor or funding agency, representatives of the IRB, regulatory agencies or representatives from companies or organizations supplying the product, may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study.

The study participant's contact information will be securely stored on a secure study database for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor/funding agency requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be stored on a secure UNC server. The study data entry and study management systems used by research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived on a secure UNC server.

Measures Taken to Ensure Confidentiality of Data Shared per the NIH Data Sharing Policies

It is NIH policy that the results and accomplishments of the activities that it funds should be made available to the public (see *https://grants.nih.gov/policy/sharing.htm*). The PI will ensure all mechanisms used to share data will include proper plans and safeguards for the protection of privacy, confidentiality, and security for data dissemination and reuse (e.g., all data will be thoroughly de-identified and will not be traceable to a specific study participant). Plans for archiving and long-term preservation of the data will be implemented, as appropriate.

Certificate of Confidentiality

To further protect the privacy of study participants, the Secretary, Health and Human Services (HHS), has issued a Certificate of Confidentiality (CoC) to all researchers engaged in biomedical, behavioral, clinical or other human subjects research funded wholly or in part by the federal government. Recipients of NIH funding for human subjects research are required to protect identifiable research information from forced disclosure per the terms of the NIH Policy (see *https://humansubjects.nih.gov/coc/index*). As set forth in 45 CFR Part 75.303(a) and NIHGPS Chapter 8.3, recipients conducting NIH-supported research covered by this Policy are

required to establish and maintain effective internal controls (e.g., policies and procedures) that provide reasonable assurance that the award is managed in compliance with Federal statutes, regulations, and the terms and conditions of award. It is the NIH policy that investigators and others who have access to research records will not disclose identifying information except when the participant consents or in certain instances when federal, state, or local law or regulation requires disclosure. NIH expects investigators to inform research participants of the protections and the limits to protections provided by a Certificate issued by this Policy.

10.1.4 FUTURE USE OF STORED DATA

Data collected for this study will be analyzed and stored on a secure UNC server. After the study is completed, the de-identified data will be made available to other researchers, available by request to the PI. Investigators requesting study data must adhere to regulatory requirements for data use (e.g., IRB approvals, data use agreements). No biological samples are collected for this study.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator	**Independent Safety Monitor**
Kelli D. Allen, PhD	Michael K. Seifert, MD Assistant Professor of Orthopaedics, Primary Care and Interventional Sports Medicine
University of North Carolina at Chapel Hill	University of North Carolina at Chapel Hill
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10.1.6 SAFETY OVERSIGHT

Because this study involves only survey-based assessments and digital recordings and participation in mild / moderate physical activity programs, this is a minimal risk study we do not believe it requires a data safety monitoring board.

Safety oversight will be under the direction of the Safety Officer (SO). The SO will be independent from the study conduct and free of conflict of interest. The SO's role is to advise the PI (and not the NIAMS) regarding participant safety, scientific integrity and ethical conduct of the study. On a biannual basis or as requested, the PI will provide to the SO a study summary, a report of all AEs, and any problems or issues that have been identified.

10.1.7 CLINICAL MONITORING

Since this is a single site study there will not be site visits conducted by the PI or co-investigators. However, we will monitor the fidelity of intervention delivery as described above. Navitas may conduct a site visit on behalf of the NIAMS, however, Navitas will not have the responsibility of the overall clinical monitoring for this study.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Quality control (QC) procedures will be implemented as follows:

Informed consent --- During the consenting process, the study team member will review the completed consent document to ensure the participant has signed and dated the consent form accurately prior to completing any other study activities.

Source documents and the electronic data --- Data from the physical function and balance will be initially captured on source documents and will ultimately be entered into the study database; all other data from study measures will be entered directly into the study database. To ensure accuracy site staff will compare a representative sample of source data against the database.

Protocol Deviations – The study team will review protocol deviations on an ongoing basis and will implement corrective actions when the quantity or nature of deviations are deemed to be at a level of concern.

Should independent monitoring become necessary, the PI will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor/funding agency, and inspection by local and regulatory authorities.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Study data will be stored on a secure UNC server in a folder accessible only to IRB-approved study team members. We will use REDCap to store all patient information and dispositions, responses to screening and outcome assessments. REDCap is a secure web application supported at UNC that can be used to build and manage case report forms, surveys, and other data capture mechanisms. Additionally, for the *OA CARE* intervention, the participant's name and contact information will be shared with the YMCA verbally by phone, by encrypted email or a UNC IRB approved platform for sharing PHI. Paper copies will be rare and if necessary will be kept to a minimum and if shared will be done via a UNC IRB approved platform for sharing PHI. Any paper copies will be stored in the participant's individual study folder, which will be kept in a locked file cabinet of a study team member.

10.1.9.2 STUDY RECORDS RETENTION

Research study records will be maintained for no less than 6 years following the completion of the study, after which time personal identifying information will be removed. Research information in a subject's medical record will be kept indefinitely. No records will be destroyed without the written consent of the sponsor/funding agency, if applicable. It is the responsibility of the sponsor/funding agency to inform the investigator when these documents no longer need to be retained.

10.1.10 PROTOCOL DEVIATIONS

This protocol defines a protocol deviation as any noncompliance with the clinical trial protocol,

ICH GCP, or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions will be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- Section 4.5 Compliance with Protocol, subsections 4.5.1, 4.5.2, and 4.5.3

- Section 5.1 Quality Assurance and Quality Control, subsection 5.1.1
- Section 5.20 Noncompliance, subsections 5.20.1, and 5.20.2.

It will be the responsibility of the site investigator to use continuous vigilance to identify and report deviations that impact participant safety to the UNC IRB within 7 business days of the time the PI becomes aware to the event, if the protocol deviation harmed participant(s) or others or placed participant(s) or others at increased risk of harm. Otherwise, protocol deviations/violations that occur but do not affect participant safety will be submitted with the routine safety reports as noted. Protocol deviations will be sent to the reviewing IRB per their policies. The site investigator will be responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the MOP. Additionally, protocol deviations impacting participant safety will be sent to the NIAMS (through the NIAMS Executive Secretary) and the SO within 48 hours of the investigator becoming aware of the event, and that the SO's feedback will be shared with the NIAMS once received.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

- National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers after the completion of the primary endpoint by contacting the study PI. Considerations for ensuring confidentiality of these shared data are described in Section 10.1.3

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the National Institute on Aging has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ADDITIONAL CONSIDERATIONS

N/A

10.3 ABBREVIATIONS

ACR	American College of Rheumatology
AE	Adverse Event

BMI	Body Mass Index
DHHS	Department of Health and Human Services
CoC	Certificate of Confidentiality
CFR	Code of Federal Regulations
EHR	Electronic Health Record
EMR	Electronic Medical Record
GCP	Good Clinical Practice
GLMM	General Linear Mixed Model
HHS	Health and Human Services
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICH	International Council on Harmonisation
IRB	Institutional Review Board
MOP	Manual of Procedures
MVPA	Moderate to Vigorous Intensity Physical Activity
NIAMS	National Institute of Arthritis and Musculoskeletal and Skin Diseases
NIH	National Institutes of Health
OA	Osteoarthritis
OAAA	Osteoarthritis Action Alliance
OARSI	Osteoarthritis Research Society International
OA CARE	OA Clinic-Community CARE Model
OHRP	Office for Human Research Protections
PA	Physical Activity
PCP	Primary Care Provider
PI	Principal Investigator
QC	Quality Control
RCT	Randomize Control Trial
SAE	Serious Adverse Event
UC	Usual Care
UNC	University of North Carolina
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index

10.4 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale
2.0	7.26.22	Revised column headers on Schedule of Activities	Revised to correspond with visits described on the Schema

3.0	09.06.22	Updated Synopsis and Strategies for Recruitment and Retention	Revised because we will also be recruiting patients from UNC Family Medicine

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