Protocol Documents

Study Protocol

Weight loss and Exercise for Communities with Arthritis in North Carolina (WE-CAN)

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Project Description:

The global prevalence of knee osteoarthritis (OA) is estimated at greater than 250 million persons or 3.6% of the world population, ranking 23rd on the list of the most common sequelae. Knee OA is the most prevalent cause of mobility dependency and disability, with the time spent living with symptoms averaging 26 years. More than two-thirds of Americans age ≥ 20 years are overweight or obese. Two in three people who are obese will develop symptomatic knee OA in their lifetime. In addition to the strong relationship between obesity and knee OA, a recent systematic review found no healthy consequences of overweight/obesity, even in individuals who are metabolically healthy.

In 2004 we reported that a 5% weight loss, when combined with exercise, resulted in a 30% decrease in pain and a 24% improvement in function. Our recently completed trial entitled Intensive Diet and Exercise for Arthritis (IDEA) sought to improve on our work with a more intensive weight loss intervention, 2 to 3 times the weight loss we had recently achieved. IDEA compared intensive diet (D) and exercise (E) interventions, separately and in combination, across an 18-month intervention period in 454 overweight and obese older adults with radiographic knee OA. An intent-to-treat analysis revealed that after 18 months the D+E group reduced pain by 51% compared to 25% and 28% for the D only and E only groups, respectively. The D+E group was also superior to the E group on self-reported physical function, health related quality of life, and walking speed, and had significantly lower knee joint loading and serum levels of IL-6, a pro-inflammatory cytokine. On average, our D+E intervention was twice as effective at relieving pain as previous long-term OA trials. We concluded that wider adoption of intensive weight loss with a goal of at least 10% of baseline body weight combined with exercise could reduce the burden of disability related to knee OA.

IDEA was an efficacy study with impressive results, a trial designed to determine the effects of intensive diet and exercise *under ideal circumstances*. However, a common concern from physicians who treat people with knee OA is lack of practical means to implement this treatment in the clinical environment. Indeed, there is no evidence regarding how this efficacious intervention could be successfully adapted to be effective in real world clinical and community settings and also be cost effective.

We plan to conduct the first long-term (18 months) pragmatic (i.e., effectiveness) trial of intensive diet and exercise in older adults with knee OA under more usual conditions in both rural and urban communities across

North Carolina. Participants (age ≥ 50 years; BMI ≥ 27 kg/m^2) will be randomized to one of 2 groups: diet-induced weight loss and exercise or an attention control group. The sample will consist of 820 ambulatory, community-dwelling persons that meet the ACR clinical criteria for knee osteoarthritis. The primary aim is to compare the intervention effects on knee pain. Secondary aims will compare the intervention effects on self-reported function, mobility, health related quality of life, and the cost effectiveness and budgetary impact of the intervention.

This program will deliver state-of-the-art weight-management techniques using procedures that are new to this area of research in a community setting. Our proposed study is innovative in at least 6 important ways.

1. ***The first long-term trial of diet-induced weight loss and exercise in adults with knee OA delivered in a practical, less rigorously monitored, community setting.*** We will design and implement this intervention to make it cost-effective and to serve as a blueprint for diverse communities nationwide. If successful, the results can inform healthcare payers about the first non-pharmacologic treatment of proven benefit for overweight and obese adults with knee OA that also promises to decrease medical care costs.
2. ***The first pragmatic behavioral health trial targeting rural and urban sites***. Few pragmatic trials have focused on rural populations (Fortney et al; Gooch et al; Schmidt et al), and none was designed to affect behavior change using community health interventionists. About 25% of the US population lives in diverse rural communities. Most have fewer services and resources than urban communities (US Dept. of Agr). They report poorer health-related quality of life (National Rural Health Assoc.), reflecting higher prevalence of many disorders, including OA. Tailoring a non-pharmacologic intervention for communities with limited healthcare access would be a breakthrough for public health (National Rural Health Assoc.).
3. ***The first evidence that this non-pharmacologic intervention can be implemented cost-effectively in US communities*.** Successful results will lead to step-by-step guidelines regarding the selection of community intervention sites, ways to engage the medical community, and how to deliver a weight-loss and exercise intervention. In addition to the well-established association between obesity and knee OA, strong relationships exist between high BMI/obesity and coronary heart disease, type 2 diabetes, high blood pressure, stroke, dyslipidemia, and certain types of cancer (Bhaskaran et al; Campbell). This trial will provide a model for community leaders to develop and execute an effective diet and exercise program at a reasonable cost that will engage local physicians and healthcare providers who treat knee OA, obesity, and related comorbidities.
4. ***A practical treatment option for physicians who treat the comorbidities associated with high BMI.*** Both the CDC and the American Cancer Society have strategic initiatives that encourage community-based interventions to effectively reduce overweight and obesity (Bauer et al; Campbell).
5. ***Focus on implementation and scalability of treatment approaches*.** The innovative features of the proposed study will bridge short-term efficacy and long-term outcomes. Identifying and applying the factors critical for intervention sustainability ensure translation from research to practice.
6. ***Formal assessment of cost-effectiveness and Budget Impact Analysis***. Although rarely performed in pragmatic trials, we will formally assess the cost-effectiveness of the implemented strategies. Results will allow clinicians and policymakers to assess the feasibility of community-based implementation

The proposed study is uniquely designed to identify a practical, effective, non-pharmacologic therapy capable of reducing knee pain and improving function and quality of life in rural and urban communities of older, overweight and obese adults with knee OA.

Primary Hypothesis and Aim

Hypothesis 1. A pragmatic, community-based, diet-induced weight-loss and exercise intervention will significantly reduce knee pain among overweight and obese adults aged ≥ 50 years with knee OA compared to an attention-control group.

Aim 1. To determine whether a pragmatic, community-based, 18-month diet-induced weight-loss and exercise intervention implemented in three North Carolina counties with diverse residential (from urban to rural) and socioeconomic composition significantly decreases knee pain [as measured by the Western Ontario McMasters Universities Osteoarthritis Index (WOMAC) pain subscale] in overweight and obese adults with knee OA compared to an attention-control group**.**

Secondary Hypotheses and Aims

Hypothesis 2. A pragmatic, community-based, diet-induced weight-loss and exercise intervention will significantly improve self-reported function, health-related quality of life, and mobility among overweight and obese adults aged ≥ 50 years with knee OA compared to an attention-control group.

Aim 2. To determine whether a pragmatic, community-based, 18-month, diet-induced weight-loss and exercise intervention improves WOMAC self-reported function, health-related quality of life as measured by the physical subscale of the SF-36 questionnaire and 6-minute walk distance (an accepted measure of mobility) in overweight and obese adults with knee OA compared to an attention control group.
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Hypothesis 3. A pragmatic, community-based, diet-induced weight-loss and exercise intervention will be a cost-effective addition to treatment modalities in overweight and obese persons with knee OA.

Aim 3. To establish the cost-effectiveness of this pragmatic, community-based, multimodal diet-induced weight-loss and exercise program by conducting cost-effectiveness and budgetary impact analyses using data from the current trial in a validated computer-simulated model of knee OA.

Study Design

We will randomize 820 overweight and obese (BMI 27 ≥ kg/m^2), adults age ≥50 yrs knee OA into one of 2 groups: an intensive dietary restriction-plus-exercise (D+E) group or an attention control group. Forsyth, Johnston, and Haywood Counties' recruitment goals are 450, 220, and 150, respectively. Our minimum weight-loss goal for the weight-loss group will be 10% of body weight. The exercise intervention will meet 2 days/wk at the clinical site and will exercise 1 day/wk at home or other location of their choice. The intervention will be comprised of both aerobic and strength training exercises. The healthy lifestyle group will meet 4 times over an 18 month period and receive a combination of webinars, emails, and mailings for the remaining months.

Primary Endpoint

Western Ontario McMasters Universities Osteoarthritis Index (WOMAC). We will measure self-reported physical function and pain using the WOMAC. The LK version asks participants to indicate on a scale from 0 (none) to 4 (extreme) the degree of difficulty experienced in the last 48 hours due to knee OA. Individual scores for the 17 items are totaled to generate a summary score that could range from 0-68, with higher scores indicating poorer function. The pain index assesses participants' pain on the same scale, ranging from 0 (none) to 4 (extreme). The pain subscale consists of 5 items and total scores can range from 0-20, with larger scores indicating greater dysfunction. This instrument has been validated and recommended by the Osteoarthritis Research Society as the health status measure of choice in older adults with knee OA.

Secondary Endpoint

Mobility. Our primary mobility measure will be 6-minute walk distance. Participants are told to walk as far as possible in 6 minutes on an established course. No personal timing devices are permitted, and participants are not provided feedback during the test. Results are significantly correlated to treadmill time and symptom-limited maximal oxygen consumption (r = 0.52 and r = 0.53, respectively) and have a 3-month test-retest reliability of 0.86 (Pennix et al). The Short Physical Performance Battery (SPPB) will also be used to measure mobility (Guralnik et al). The SPPB is comprised of the following tests (balance, walking speed, and chair rise).

Cost Effectiveness Resource utilization will be collected by questionnaire, with domains including visits to

clinicians (physicians, nurses, physical therapists, others), tests, medications, injections, surgery, alternative therapies. The Work Productivity and Activity Impairment index (WPAI) will be used to assess absenteeism and reduced productivity while at work (presenteeism).

Body weight, height, hip/waist circumference, BMI. Body weight and height will be obtained using standard techniques. Only persons with a BMI ≥ 27 kg/m^2 will be eligible.

Medical History and Medications. Participants will be given forms to assess medical history and presence of comorbidities. Participants will also be asked questions about their medical history during the phone screen so as to reduce participant burden by identifying potential exclusion criteria. Participants will be administered a medication questionnaire adapted from the ARIC study and widely used in field research and in our prior studies at each testing visit (ARIC).

It is designed to obtain information about all prescription and over-the-counter medicines and supplements used during the 2 weeks prior to the interview (home or clinic). The participants will be mailed the medication form to fill out at home and will return the form to the interviewer. Participants may also be asked to provide the interviewer with all medicine containers so that the interviewer can transcribe the information. In addition participants will be encouraged to notify the study staff of any medication changes during the course of the study.

In addition to the medical history and medication questionnaires, participants will also be given a risk stratification questionnaire at the first screening visit. The purpose of this questionnaire is to divide participants into 3 levels of cardiovascular risk: low, moderate, and high. Risk stratification is based in the presence/absence of cardiovascular disease risk factors, sign and symptoms, and known medical history. The American College of Sports Medicine recommends that patients who are at moderate risk receive medical clearance if they are to begin a vigorous exercise program but that medical clearance is not needed for moderate intensity exercises (Pescatello et al., 2014). We have made a slight adjustment to the protocol so that all participant exercise falls within this moderate intensity range. Specifically, the original protocol called for participants to exercise in the range of 50-75% of their maximal heart rate reserve (i.e., moderate to high intensity). This range has been modified to 40-60% of maximal heart rate reserve (i.e., moderate intensity). Hence, participants that fall into the low and moderate risk category will be allowed entry into the study without the need for physician clearance. *Those who fall within the high risk category will require medical clearance from their physician.* Final approval and acceptance into the program for high risk patients will be provided by our study physician. It's worth noting the risk of serious adverse events occurring during properly supervised exercise is extremely low (< 1 per 100,000 hours of exercise) even in older adults, with cardiovascular disease.

Measures of Quality of Life. The SF-36 is the most widely used and carefully validated measure of health related quality of life and will be used to yield 2 broad summary scores: physical health and mental health (Ware and Sherbourne). The Eurqol Quality of Life will also be used to measure quality of life. The Adherence Self Efficacy questionnaire is designed to assess beliefs in one's ability (confidence) to continue exercising at various intensities and frequencies. The FAST-23 will be used to measure physical disability.

Dietary Intake. National Cancer Institute Modified Health Habits and History Questionnaire (HHHQ) provides nutrient assessment of dietary intake.

Physical Activity. The Physical Activity Scale for the Elderly (PASE) has proven reliable in many of our clinical trials, including a group of 254 men and women aged ≥65 yrs (Washburn et al).

Cognitive Functioning. The MOCA will be used to measure cognitive function (Nasreddine et al).

Inclusion/Exclusion Criteria

Inclusion Criteria:

(1) Age ≥ 50 years

(2) Knee Pain plus ACR Criteria for Knee Osteoarthritis

(3) BMI = 27 ≥ kg/m^2

Exclusion Criteria:

1. Significant co-morbid disease that would threaten safety or impair ability to participate in interventions or testing (Method: Medical history; medications; physical exam; telephone pre-screen; risk stratification)
    a. Blindness
    b. Type 1 diabetes
    c. Other type of arthritis (rheumatoid, psoriatic, fibromyalgia, etc.)
    d. History or symptoms of coronary artery disease or pulmonary disease with no medical clearance (symptoms include angina, unreasonable breathlessness, dizziness/fainting/blackouts)
    e. Unable to walk without a device
2. Not sufficiently overweight or obese, BMI < 27 kg/m^2 (Method: Ht/Wt)
3. Not having knee pain: (Method: ≤ 4 on the pain scale, WOMAC and Telephone Screen)
4. Inability to finish 18-month study or unlikely to be compliant (Method: Telephone Screen, Screening Interviews)
    a. Planning to leave area > 2 month during the next 18 months
    b. Unwilling to change eating or physical activity habits
    c. Unwilling to attend exercise/diet sessions
5. Age, age < 50 (Method: Telephone Screen & Demographics Forms)
6. Other conditions that may prohibit the effective delivery of the intervention (Method: Telephone Screen)
    a. Unable to provide own transportation to exercise center
    b. Unable to read or write, cannot speak or read English

Randomization Procedures

We propose a stratified block randomization with block size unknown to investigators and staff will ensure equal accrual to each study arm. Prestratification will balance pretrial BMI values (27.0-34.9 kg/m^2, 35.0-44.9 kg/m^2, ≥45 kg/m^2) and gender, which could predict intervention effect and associations between secondary outcome variables. We will also use county as a fixed effect for randomization. A computer program will randomize participants into the 2 groups, verify eligibility, and provide identification number and intervention assignment. This system worked very successfully in the IDEA study.

Interventions

Diet-induced weight loss plus exercise

Months 0 -6

There will be two individual sessions per month and 2 group sessions per month for the first 6 months. The behavioral sessions will focus on awareness of changing eating habits to lower caloric intake. Educational content information regarding what food changes to make, how to make them, and why they are important will be clearly explained and discussed with participants and significant others. Each group session will include problem solving, review of a specific food topic, and tasting of several well-balanced, low-fat, nutritious foods prepared with widely available ingredients. During the individual sessions, the counselor will review individual progress, solve problems, answer questions, and set goals. During the initial individual session, the nutrition counselor will give the participant a weight history background questionnaire. The major emphasis for Period 1 is to enhance participant awareness of the importance and the need to change eating habits, i.e. lower caloric intake for weight loss. Each participant should be given the opportunity to practice skills using goal setting in a stepwise approach. Participants will follow a weekly menu plan which will incorporate meal replacements into their diet plan. Lean Shakes, a General Nutrition Center (GNC), product will be the meal replacement used. Participants may replace the Lean Shakes with a healthy, low-calorie meal of their choice, such as Lean Cuisine. Motivation and encouragement through the combined efforts of the nutrition counselor, the participant, significant others and the nutrition staff will enhance adherence.

Months 7-12

In period 2 participants will focus on continued weight loss to reach the study weight loss goal of 10% of baseline weight. Participants will attend one group and one individual session per month. Once the weight loss goal is achieved an individual may either begin weight maintenance, or they may continue to lose additional weight using safe and healthy nutrition practices. Participants will follow a weekly menu plan with recipes using traditional foods and the option to incorporate meal replacements. The traditional meals will contain 400-600 kcals, be low in fat and added sugars, and high in vegetables, fruits, and whole grains. Snacks may be a bar, fruit, or vegetable providing ~100-120 kcals. Daily caloric intake for each participant will be adjusted to his or her rate of weight change. Each group will be encouraged to take a daily multivitamin/mineral supplement containing no more than 100% of the Dietary Reference Intake for any particular nutrient. As fewer meal replacements are consumed, intervention staff will assist in developing meal plans to provide the prescribed macronutrient-balanced energy intake.

Months 13-18

Period 3 will emphasize weight management over time, with 1 monthly group contact. Weight loss can continue throughout the intervention, provided the participant wants to and has not reached a level associated with health hazards; i.e. a 20% body weight loss at 6 months or >30% at 12 months. Participants will continue to follow a weekly menu plan with recipes using traditional foods and the option to incorporate meal replacements.

The exercise intervention will cover an 18-month period. The exercise program will consist of a 15-minute aerobic phase, a 20-minute strength-training phase, a second 15-minute aerobic phase, and a 10-minute cool-down phase. These sixty-minute exercise sessions will be conducted three days per week (two days/week will be center based). Each participant will be prescribed an individual walking prescription by the exercise leader, which will be adjusted accordingly, as each participant progresses throughout the 18 months. The exercise will be of moderate intensity. Alternate forms of aerobic exercise, such as but not limited to stationary bike, elliptical trainer, or treadmill walking, can be used in place of over-ground walking. This choice could be based on participant preference, the limitations of the exercise facility, or the participant's pain level.

Intervention Locations: *Forsyth County:* The diet and exercise classes will be offered at a number of sites within Winston-Salem. Participants will be allowed to pick the location that is most convenient for them to attend. Classes will take place at the Clinical Research Center on the Wake Forest University Campus, at St. Peter's World Outreach Center, and at Smiley's Fitness. *Haywood County:* The diet and exercise classes will be held at the Medwest Health & Fitness Center in Waynesville, NC. *Johnston County:* The diet and exercise classes will be held at the Clayton Community Center and the Johnston Medical Mall.

All intervention staff in the WE-CAN study will be CPR certified. The exercise coordinator, who is part of the coordinating center and is responsible for maintaining exercise protocol congruity between the intervention sites, will train and supervise the intervention staff. Intervention staff will meet monthly with the exercise coordinator to discuss any potential problems, risks, and concerns that have risen. AEDs will be available at each location. Emergency drills will be performed monthly in addition the AED will be checked monthly. The clinical research center (Forsyth), Johnston Medical Mall (Johnston), and the Medwest Health and Fitness Center (Haywood) also house cardiac rehabilitee programs and will also have crash carts available.

Attention Control Intervention

The attention control intervention will cover an 18-month period. There will be four total face to face group meetings over the 18 months, with one meeting each at months 1, 6, 12, and 18; and during the other months (months 2-5, 7-11, 13-17) participants will receive a combination of informational packets, webinars, and emails. Each group meeting will last approximately one hour and will be held at Senior Services in Winston-Salem, NC. The sessions will be interactive and will provide useful information on such topics as proper foot care, general nutrition, management of medications, and sleep practices. The Community Advisory Board will give input on the class sessions. The final component of the workshop, the upper body stretching component, was chosen to be part of the control arm to enhance adherence to this arm of the study. Specifically, this "placebo exercise" activity will serve to increase the benefit perceived by the participants without directly affecting the study outcomes. Hand-outs for upper body stretching at home will be provided. Prior studies of middle aged to older adults suggest that participants will be less likely to participate if they think that any of the treatment groups will not provide personal benefit. These stretching exercises will be restricted to the upper body and have not been shown to have an influence on the primary study outcomes.

For the other months, experts across a broad range of relevant topics that are of interest to older adults will provide information via information packets, webinars or emails. These monthly contacts and email blasts will keep the participants in the attention control group engaged in the WE-CAN study and will increase adherence to the group sessions and the testing visits.

Procedures-Screening and Follow-up Visits.

Measurements	PSV	SV1	FU6	FU12	FU18	Explanation
Questionnaires						
Informed Consent		x				
Eligibility Questionnaire	x					To determine eligibility
Medical History	xc	x	x	x	x	For eligibility and to document changes in health
Comorbidities Questionnaire		x	x	x	x	
ACSM Risk Stratification	xc	x				For eligibility

Randomization		x				
WOMAC		x	x	x	x	Pain is primary and function secondary outcomes
Cost Effectiveness		x	x	x	x	
PASE scale		x	x	x	x	Physical Activity Scale for the Elderly
MOCA		x			x	Montreal Cognitive Assessment
EuroQol Quality of Life(EQ5D)		x	x	x	x	Quality of life measure
Work History Resource		x	x	x	x	Visits to clinicians, tests, medications, injections, surgery, alternative therapies
Work Productivity and Activity Impairment Index		x	x	x	x	assesses absenteeism and presenteeism
DHQ II		x	x	x	x	NIH Diet History Questionnaire
SF-36		x	x	x	x	Health related quality of life (physical, mental)
Self-Efficacy-Adherence		x	x	x	x	Belief can exercise at various intensities
Demographics		x				
Medication form		x	x	x	x	Atherosclerosis Risk in Communities form
Adverse Events			x	x	x	Also collected as they occur
Physical Performance Tests/Knee Exam						
height	xc	x				To determine BMI
weight	xc	x	x	x	x	To determine BMI
Knee exam		x				To determine eligibility
6 minute walk		x	x	x	x	Measure of mobility
Short Physical Performance Battery (SPPB)		x	x	x	x	Gait speed, sit to stand, balance tests; predicts disability
Functional Leg Strength		x	x	x	x	Sit to stand test, part of SPPB
xc = brief screen by self-report, PSV = Prescreening Visit. SV = screening visit. FU = follow-up.						

Procedures-Screening and Follow-up Visits.

Prescreening visit (PSV). Individuals who contact our recruitment office in response to advertising will be asked a series of brief questions that focus on major eligibility criteria. A screening visit appointment will be made for participants who meet major eligibility criteria. A medical history form and a medication form will be mailed to the participants for them to complete.

d.5.Screening Visit One (SV1) Individuals will come to Reynolds Gymnasium on the campus at Wake Forest University. SV1 includes an explanation of the study and obtaining informed consent. Other assessments include medical history and medication use (previously mailed), cardiovascular risk, height and weight (to calculate BMI), and a knee exam. The MOCA will be administered. The following questionnaires will be given: demographics, cost effectiveness questionnaires, WOMAC, Physical Activity Scale for the Elderly (PASE), Health-Related Quality of Life (HRQL), dietary intake questionnaires, and efficacy measures. At the end of the visit the SPPB and 6 minute walk will be performed. This screening visit will last approximately 1.5-2 hours.

6-month Follow-up Data Collection Visit (FU6): Participants will return to Reynolds Gym to repeat all measures collected at baseline (minus the MOCA and demographics). The testing session will last approximately 1.5 – 2 hours.

12-month Follow-up Data Collection Visit (FU12): Participants will return to Reynolds Gym to repeat all measures collected at baseline (minus the MOCA and demographics). The testing session will last approximately 1.5 – 2 hours.

18-month Follow-up Data Collection Visit (FU18): Participants will return to Reynolds Gym to repeat all measures collected at baseline (minus the demographics). The testing session will last approximately 1.5 – 2 hours.

Safety Monitoring Plan

A safety committee has been established to monitor participant safety and to evaluate the progress of the study.

Adverse Event and Serious Adverse Event Collection and Reporting

Adverse Event (AE) - An AE is any unfavorable and unintended diagnosis, sign (including an abnormal

laboratory finding), symptom, or disease temporarily associated with the study intervention, which may or may not be related to the intervention, including excessive delayed onset muscle soreness (DOMS) as some minimal muscle soreness will be expected after the training session. AEs include any new events not present during the pre-intervention period or events that were present during the pre-intervention period which has increased in severity. Participants will be asked if any events have occurred prior to each intervention class and testing session.

Study staff will report non-serious adverse events (related and unrelated to the study) to site project manager and principal investigator within 7 days of notification of the event and will be reported to the coordinating center quarterly. Testing staff will inquire about adverse events prior to testing to ensure there are no unreported events. The site physician/PA will review non serious adverse events (AE) on a weekly basis. Non serious adverse events will be included in the NIAMS safety report and submitted bi-annually.

Serious Adverse Event (SAE) - An SAE is any untoward medical occurrence that results in death, is life-threatening, requires or prolongs hospitalization, causes persistent or significant disability/incapacity, results in congenital anomalies/birth defects, or, in the opinion of the investigators, represents other significant hazards or potentially serious harm to research participants or others.

Staff will report serious adverse events (related and unrelated to the intervention) to the site project manager and principal investigator within 24 hours of notification. Serious adverse events (SAEs) will also be reported to the site physician/PA within 24 hrs of study notification. SAEs will be reported to the coordinating center within 24 hrs of notification of the site PI. SAEs will be reported to NIAMS within 24 hours of being reported to the PI. The WFU IRB does not require the reporting of adverse events unless it is serious, unexpected and related to the study. Follow-up information will be provided to the PI, DSMB/Safety Officer, and IRB, as appropriate.

NIAMS will assign a Data Safety Monitoring Board (DSMB) or safety monitor to monitor all aspects of the study.

The DSMB/Safety Monitor will have the following charges:
• To review the entire study protocol, the operations manual, and the informed consent and assent forms for recruitment, randomization, intervention, participant safety, data management, auditing plans for participant records, and quality control and analysis plans, and to identify needed modifications.
• To review data related to efficacy, recruitment, randomization, compliance, retention, protocol adherence, trial operating procedures, forms completion, intervention effects, gender and minority inclusion, and participant safety over the course of the trial.
• To identify problems related to safety over the course of the study and to report them in writing to the PIs, who will ensure that the appropriate individuals receive the report.
• To identify a need for additional data relevant to safety and to request them from investigators.
• To propose appropriate analyses and periodically review developing data on safety and endpoints.
• To make recommendations regarding recruitment, intervention effects, retention, compliance, safety, and continuation of the study.
• To send the Program Administrator and PIs written reports following each DSMB meeting, addressing all issues raised, and subsequently sent to the IRB.
• At any time, the DSMB may recommend discontinuation of any component/intervention of the study for any of the following reasons:
1) Compelling evidence from this or any other study of an adverse effect sufficient to override any potential benefit of the interventions to the target population.
2) Compelling evidence from this or any other study of a significant beneficial effect whose continued denial to other study group(s) would be unethical.
3) A very low probability of addressing the study hypothesis within a feasible time frame.

Statistical Considerations

Data Management

The Data Management Group, part of the Coordinating Center, has primary responsibility for randomization

and analyzing data generated by the clinical centers. Data will be collected on hard-copy forms at each site and transformed to an electronic database. Our web-based management system will assure integrity and validity. Dynamic reports and periodic statistical analyses will monitor quality. A participant-based inventory system will track recruitment, retention, adherence, and missing data from entry through exit, close-out, and lock-down of final datasets. Our team developed a similar database for the IDEA and START studies.

Statistical Analyses

Statistical analyses will be conducted according to intention-to-treat principles using SAS.

Primary Aim.

The primary hypothesis of long-term reduced WOMAC pain at 18 months will be tested based on a two-tailed significance level of 0.05 using contrast statements from a repeated measures mixed linear model with time (6, 18 mos), randomization arm (D+E vs control), and the interaction, which adjusts the means at each time point for potential missing data bias (Laird and Ware). Intervention-effect estimates will be further adjusted for baseline pain values, BMI, county, and gender; analysis will match design, so the variance estimate will not be biased. Participant ID number will be included as a random effect to control for within-subject variability, and the longitudinal model will use an unstructured covariance matrix. In the unlikely event the model does not converge, a first-order autoregressive (AR[1]) covariance structure will be fit instead. Maximum-likelihood techniques will estimate parameters, as in the IDEA trial (Messier et al). Preliminary analyses will be conducted to check the shape of the distributions and variances between groups and as a function of the covariates. Regression diagnostics and residual plots will help to find appropriate transformations, if necessary. We will include exploratory analyses of subgroups, defined by gender, age (<70 vs ≥70 years), baseline BMI (27.0-34.9, 35-44.9, ≥45 kg/m^2), county, and race to determine any differential pain responses.

Secondary Aims

Repeated measures mixed linear models similar to Aim 1 will be used to analyze WOMAC function, 6-minute walk, and SF-36 physical subscale. Each outcome will be modeled separately, and 18-month effectiveness will be tested based on a two-tailed significance level of 0.05. The model will include the fixed effects study arm, time, time-group interaction, county, gender, baseline BMI, and baseline values of the outcome; participant ID number will be included as a random effect, and an unstructured covariance will be used assuming model convergence is not a problem (AR[1] otherwise). Preliminary analyses will be conducted to check the shape of the distributions and variances between groups and as a function of the covariates. Regression diagnostics and residual plots will help to find appropriate transformations, if necessary.

Missing Data

If missing data are related to outcomes, our results could be biased. Our models will include variables from previous visits determined to predict loss to satisfy Little and Rubin's conditions for data considered missing at random (MAR). If "informative censoring" occurs, we will compare analyses using subjects with complete data, multiple imputations, or explicit modeling of the censoring mechanism (Conaway, 1993, Wu and Bailey, 1989).

Primary Outcomes

Aim 1. A total sample of 820 (410/group) will provide 94% statistical power to detect differences ≥15% in pain at the 2-sided 0.05 significance level with 80% retention (2-sample t-test, Nquery Advisor). Based on ADAPT (Messier et al). The D+E group in IDEA reduced pain by an average of 51%. This approach utilizes the conditional variance approach of Borm et al. for theestimation of power for ANCOVA models using group standard deviation $\sigma = 3.50$, Pearson correlation between baseline and 18-month pain score of $\rho = 0.4$ for a conditional standard deviation $\sigma_c = 3.21$ ($\sigma_c = \sqrt{1-\rho^2} \times \sigma$), and 18-month treatment WOMAC pain means ~D+E = 5.03 vs E-only control = 5.92 (Δ = -0.887). Variations of anticipated power due to modifications in retention and treatment effect are presented in Table 1. Correlation between baseline and 18 month pain values are estimated from the IDEA trial, while anticipated treatment effects and standard deviation for pain were obtained using weighted averages of D+E and non-D+E treatments from the ADAPT and IDEA studies, with some attenuation of the anticipated treatment effect due to the pragmatic nature of WE-CAN (Table 1).

Table 1: Power estimates for WOMAC pain, assuming baseline N=820, correlation between BL and 18 months=0.4, and common group SD = 3.50.

18 month Control Mean WOMAC	18 Month D+E WOMAC Pain (% difference from	18-Month Retention					
							85%
	Anticipated 18m	81%	Standard		84%	D+E Mean (% change	86%	88%
Variable	5.03 (15%) control mean*		Deviation	ρ		from C)		
5.92		91%			92%		94%	95%
WOMAC Function	4.91 (17%)	17.5	11.5	0.6		15.3 (-12.3%)		
		96%			97%		97%	98%
Mobility: 6-Minute Walk (m)		509	90.7	0.7		524 (3.0%)		492
SF-36 Physical Score (0-100)		42.0	10.1	0.5		44.1 (4.9%)		493

Table 2: Detectable absolute and relative (%) differences for secondary outcomes, n = 410/group, 80% retention, 85% statistical power, α = 0.05. Correlation between baseline and 18M values is ρ.

494

Secondary Outcomes

Aim 2. Our sample size provides a moderate effect size of 0.234 at 85% power with relevant detectable differences. However, all estimates from IDEA and ADAPT were collected under rigorously controlled conditions; therefore the estimates for the pragmatic trial are conservative. We assume in Table 8 a total baseline sample size of N=820, 80% retention at 18 months, and a 0.05 level of significance for all tests. The detectable and % differences from control aim to achieve 85% power. The mean differences in WOMAC function for D+E compared to D only and E only in IDEA were -3.3 and -4.3, respectively. Likewise, the differences in 6-minute walk distance for the D+E group versus D only in IDEA and ADAPT (41.5 and 42.1, respectively) indicate that the mean difference to achieve 85% power (15.2 m) is modest. IDEA indicated that SF-36 physical subscale was significantly improved in the D+E arm, with an observed difference of 2.8 compared to E alone (Table 2).

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Study Protocol with Final Amendments

Weight loss and Exercise for Communities with Arthritis in North Carolina (WE-CAN)

8/26/20

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Project Description:

The global prevalence of knee osteoarthritis (OA) is estimated at greater than 250 million persons or 3.6% of the world population, ranking 23rd on the list of the most common sequelae. Knee OA is the most prevalent cause of mobility dependency and disability, with the time spent living with symptoms averaging 26 years. More than two-thirds of Americans age ≥ 20 years are overweight or obese. Two in three people who are obese will develop symptomatic knee OA in their lifetime. In addition to the strong relationship between obesity and knee OA, a recent systematic review found no healthy consequences of overweight/obesity, even in individuals who are metabolically healthy.

In 2004 we reported that a 5% weight loss, when combined with exercise, resulted in a 30% decrease in pain and a 24% improvement in function. Our recently completed trial entitled Intensive Diet and Exercise for Arthritis (IDEA) sought to improve on our work with a more intensive weight loss intervention, 2 to 3 times the weight loss we had recently achieved. IDEA compared intensive diet (D) and exercise (E) interventions, separately and in combination, across an 18-month intervention period in 454 overweight and obese older adults with radiographic knee OA. An intent-to-treat analysis revealed that after 18 months the D+E group reduced pain by 51% compared to 25% and 28% for the D only and E only groups, respectively. The D+E group was also superior to the E group on self-reported physical function, health related quality of life, and walking speed, and had significantly lower knee joint loading and serum levels of IL-6, a pro-inflammatory cytokine. On average, our D+E intervention was twice as effective at relieving pain as previous long-term OA trials. We concluded that wider adoption of intensive weight loss with a goal of at least 10% of baseline body weight combined with exercise could reduce the burden of disability related to knee OA.

IDEA was an efficacy study with impressive results, a trial designed to determine the effects of intensive diet and exercise *under ideal circumstances*. However, a common concern from physicians who treat people with knee OA is lack of practical means to implement this treatment in the clinical environment. Indeed, there is no

evidence regarding how this efficacious intervention could be successfully adapted to be effective in real world clinical and community settings and also be cost effective.

We plan to conduct the first long-term (18 months) pragmatic (i.e., effectiveness) trial of intensive diet and exercise in older adults with knee OA under more usual conditions in both rural and urban communities across North Carolina. Participants (age ≥ 50 years; BMI ≥ 27 kg/m^2) will be randomized to one of 2 groups: diet-induced weight loss and exercise or an attention control group. The sample will consist of 820 ambulatory, community-dwelling persons that meet the ACR clinical criteria for knee osteoarthritis. The primary aim is to compare the intervention effects on knee pain. Secondary aims will compare the intervention effects on self-reported function, mobility, health related quality of life, and the cost effectiveness and budgetary impact of the intervention.

This program will deliver state-of-the-art weight-management techniques using procedures that are new to this area of research in a community setting. Our proposed study is innovative in at least 6 important ways.

7. ***The first long-term trial of diet-induced weight loss and exercise in adults with knee OA delivered in a practical, less rigorously monitored, community setting.*** We will design and implement this intervention to make it cost-effective and to serve as a blueprint for diverse communities nationwide. If successful, the results can inform healthcare payers about the first non-pharmacologic treatment of proven benefit for overweight and obese adults with knee OA that also promises to decrease medical care costs.
8. ***The first pragmatic behavioral health trial targeting rural and urban sites***. Few pragmatic trials have focused on rural populations (Fortney et al; Gooch et al; Schmidt et al), and none was designed to affect behavior change using community health interventionists. About 25% of the US population lives in diverse rural communities. Most have fewer services and resources than urban communities (US Dept. of Agr). They report poorer health-related quality of life (National Rural Health Assoc.), reflecting higher prevalence of many disorders, including OA. Tailoring a non-pharmacologic intervention for communities with limited healthcare access would be a breakthrough for public health (National Rural Health Assoc.).
9. ***The first evidence that this non-pharmacologic intervention can be implemented cost-effectively in US communities.*** Successful results will lead to step-by-step guidelines regarding the selection of community intervention sites, ways to engage the medical community, and how to deliver a weight-loss and exercise intervention. In addition to the well-established association between obesity and knee OA, strong relationships exist between high BMI/obesity and coronary heart disease, type 2 diabetes, high blood pressure, stroke, dyslipidemia, and certain types of cancer (Bhaskaran et al; Campbell). This trial will provide a model for community leaders to develop and execute an effective diet and exercise program at a reasonable cost that will engage local physicians and healthcare providers who treat knee OA, obesity, and related comorbidities.
10. ***A practical treatment option for physicians who treat the comorbidities associated with high BMI.*** Both the CDC and the American Cancer Society have strategic initiatives that encourage community-based interventions to effectively reduce overweight and obesity (Bauer et al; Campbell).
11. ***Focus on implementation and scalability of treatment approaches.*** The innovative features of the proposed study will bridge short-term efficacy and long-term outcomes. Identifying and applying the factors critical for intervention sustainability ensure translation from research to practice.
12. ***Formal assessment of cost-effectiveness and Budget Impact Analysis***. Although rarely performed in pragmatic trials, we will formally assess the cost-effectiveness of the implemented strategies. Results will allow clinicians and policymakers to assess the feasibility of community-based implementation

The proposed study is uniquely designed to identify a practical, effective, non-pharmacologic therapy capable of reducing knee pain and improving function and quality of life in rural and urban communities of older, overweight and obese adults with knee OA.

Primary Hypothesis and Aim

Hypothesis 1. A pragmatic, community-based, diet-induced weight-loss and exercise intervention will significantly reduce knee pain among overweight and obese adults aged ≥ 50 years with knee OA compared to an attention-control group.

Aim 1. To determine whether a pragmatic, community-based, 18-month diet-induced weight-loss and exercise intervention implemented in three North Carolina counties with diverse residential (from urban to rural) and socioeconomic composition significantly decreases knee pain [as measured by the Western Ontario McMasters Universities Osteoarthritis Index (WOMAC) pain subscale] in overweight and obese adults with knee OA compared to an attention-control group**.**

Secondary Hypotheses and Aims

Hypothesis 2. A pragmatic, community-based, diet-induced weight-loss and exercise intervention will significantly improve self-reported function, health-related quality of life, and mobility among overweight and obese adults aged ≥ 50 years with knee OA compared to an attention-control group.

Aim 2. To determine whether a pragmatic, community-based, 18-month, diet-induced weight-loss and exercise intervention improves WOMAC self-reported function, health-related quality of life as measured by the physical subscale of the SF-36 questionnaire and 6-minute walk distance (an accepted measure of mobility) in overweight and obese adults with knee OA compared to an attention control group.
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Hypothesis 3. A pragmatic, community-based, diet-induced weight-loss and exercise intervention will be a cost-effective addition to treatment modalities in overweight and obese persons with knee OA.

Aim 3. To establish the cost-effectiveness of this pragmatic, community-based, multimodal diet-induced weight-loss and exercise program by conducting cost-effectiveness and budgetary impact analyses using data from the current trial in a validated computer-simulated model of knee OA.

Study Design

We will randomize 820 overweight and obese (BMI 27 ≥ kg/m^2), adults age ≥50 yrs knee OA into one of 2 groups: an intensive dietary restriction-plus-exercise (D+E) group or an attention control (nutrition and health) group. Persons who have begun screening once we hit our overall recruitment goal of 820 will be allowed to complete the screening process therefore up to 840 persons may be enrolled into the study. Forsyth, Johnston, and Haywood Counties' recruitment goals are 420, 210, and 210, (total 840) respectively. Our minimum weight-loss goal for the weight-loss group will be 10% of body weight. The exercise intervention will meet 3 days/wk at the clinical site. The intervention will be comprised of both aerobic and strength training exercises. When participants are unable to come into the facility for intervention, sessions will be conducted via phone or through video conferencing. The nutrition and health group will meet 5 times over an 18 month period and receive a combination of webinars, video messages, text messages, emails (via personal email or Facebook), phone calls, and mailings for the remaining months. Participants will be allowed to choose their preferred method.

Primary Endpoint

Western Ontario McMasters Universities Osteoarthritis Index (WOMAC). We will measure self-reported physical function and pain using the WOMAC (scores will be pulled from the KOOS Questionnaire in which the WOMAC is embedded). The LK version asks participants to indicate on a scale from 0 (none) to 4 (extreme) the degree of difficulty experienced in the last week due to knee OA. Individual scores for the 17 items are totaled to generate a summary score that could range from 0-68, with higher scores indicating poorer function. The pain index assesses participants' pain on the same scale, ranging from 0 (none) to 4 (extreme). The pain subscale consists of 5 items and total scores can range from 0-20, with larger scores indicating greater dysfunction. This instrument has been validated and recommended by the Osteoarthritis Research Society as the health status measure of choice in older adults with knee OA. In order to measure the minimal clinically improvement difference (MCID) participants will be asked to compare their knee pain to how it was at the beginning of the study.

Secondary Endpoint

Mobility. Our primary mobility measure will be 6-minute walk distance. Participants are told to walk as far as possible in 6 minutes on an established course. No personal timing devices are permitted, and participants are not provided feedback during the test. Results are significantly correlated to treadmill time and symptom-limited maximal oxygen consumption ($r = 0.52$ and $r = 0.53$, respectively) and have a 3-month test-retest reliability of 0.86 (Pennix et al). The Short Physical Performance Battery (SPPB) will also be used to measure mobility (Guralnik et al). The SPPB is comprised of the following tests (balance, walking speed, and chair rise). A test of ascending and descending stair activity measured by the time (in seconds) it takes to ascend and descend a flight of 8 steps with 20cm (8 inch) step height and handrail will also be performed.

Cost Effectiveness Resource utilization will be collected by questionnaire, with domains including visits to clinicians (physicians, nurses, physical therapists, others), tests, medications, injections, surgery, alternative therapies. The Work Productivity and Activity Impairment index (WPAI) will be used to assess absenteeism and reduced productivity while at work (presenteeism).

Body weight, height, hip/waist circumference, BMI. Body weight and height will be obtained using standard techniques. Only persons with a BMI ≥ 27 kg/m^2 will be eligible. Circumference measurements will be collected using standard techniques.

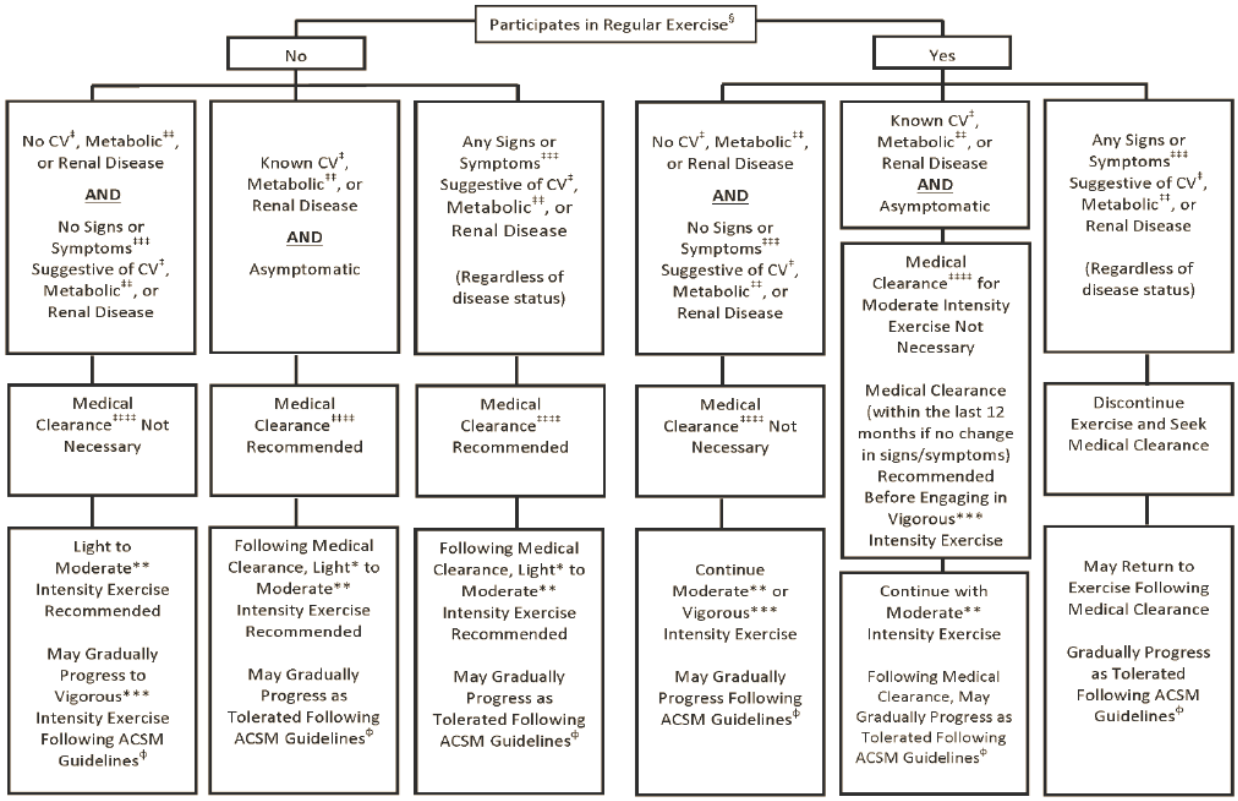
Medical History, Medications, and Blood Pressure. Participants will be given forms to assess medical history and presence of comorbidities. Participants will also be asked questions about their medical history during the phone screen so as to reduce participant burden by identifying potential exclusion criteria. Participants will be administered a medication questionnaire adapted from the ARIC study and widely used in field research and in our prior studies at each testing visit (ARIC).

It is designed to obtain information about all prescription and over-the-counter medicines and supplements used during the 2 weeks prior to the interview (home or clinic). The participants will be mailed the medication form to fill out at home and will return the form to the interviewer. Participants may also be asked to provide the interviewer with all medicine containers so that the interviewer can transcribe the information. In addition participants will be encouraged to notify the study staff of any medication changes during the course of the study.

In addition to the medical history and medication questionnaires, participants will also be given a risk stratification questionnaire at the first screening visit. The purpose of this questionnaire is to determine if participants will need medical clearance prior to enrolling into an exercise program. The determination is based on the presence/absence of cardiovascular/pulmonary/metabolic disease risk factors, sign and symptoms, and known medical history. The following schematic demonstrates how medical clearance will be determined (Figure 1). The American College of Sports Medicine recommends that all patients are first screened to

determine if they are participate in regular exercise (defined as performing planned, structured physical activity at least 30 min at moderate intensity on at least 3 days per week for at least the last 3 months). If the participant responds with no medical clearance will be not be needed for those who have not been diagnosed with any CV, Metabolic, or renal disease and are showing no signs/symptoms. If the response is yes those who have not been diagnosed as well as those with a diagnosis and are asymptomatic will not need physician clearance (Riebe et al., 2015). Like the previous recommendations this is only for moderate intensity exercise. Our exercise protocol falls within this moderate intensity range. The original protocol called for participants to exercise in the range of 50-75% of their maximal heart rate reserve (i.e., moderate to high intensity). The range was previously modified to 40-60% of maximal heart rate reserve (i.e., moderate intensity). Hence, participants that have no diagnosis of CV, Metabolic, or renal disease or those that have been diagnosed but are asymptomatic will be enrolled without the need for physician clearance. *Those who have signs and symptoms or who have been diagnosed but do not meet the exercise criteria will require medical clearance from their physician.* Final approval and acceptance into the program for patients will be provided by our study physician. It's worth noting the risk of serious adverse events occurring during properly supervised exercise is extremely low (< 1 per 100,000 hours of exercise) even in older adults, with cardiovascular disease. Blood pressure will also be measured.

Figure 1: Exercise preparticipation health screening logic model for aerobic exercise participation (Updating ACSM's Recommendations for Exercise Preparticipation Health Screening, MSSE 2015)



Measures of Quality of Life and Self-Efficacy. The SF-36 is the most widely used and carefully validated measure of health related quality of life and will be used to yield 2 broad summary scores: physical health and mental health (Ware and Sherbourne). The Eurqol Quality of Life will also be used to measure quality of life and health state (Brooks; EuroQuol). The walking efficacy for duration scale measures one's ability to walk/jog at a moderately fast pace for various durations (McAuly and Mihalko). The Positive and Negative Affect

(PANAS) measures both positive and negative affect, leading to more insightful outlooks regarding participants' feeling states. This scale consists of 20 items that reflect the intensity of how the participant "feels" right now (Watson et al). The gait efficacy/environmental efficacy scale will ask the participants' confidence in performing certain activities (McAuley et al.). Among the various components of subjective well-being, the Satisfaction with life scale is focused to assess global life satisfaction (Diener et al). The Weight Efficacy Lifestyle Questionnaire (WEL) is a 20-item measure employed to assess self-efficacy for weight management (Clark et al). The Perceived Stress Scale (PSS) will measure the degree to which people perceive their lives as stressful (Cohen et al). The adherence self-efficacy questionnaire is designed to assess beliefs in one's ability (confidence) to continue exercising at various intensities and frequencies (McAuly and Mihalko).

Pain Catastrophizing Scale (PCS). The PCS questionnaire will be used to assess catastrophizing (rumination, magnification, and helplessness) (Sullivan et al).

Knee injury and Osteoarthritis Outcome Score (KOOS). The KOOS questionnaire will be used to assess the patient's opinion about their knee and associated problems. The KOOS evaluates both short-term and long-term consequences of knee injury and also consequences of primary osteoarthritis (OA) (Roos & Lohmander).

Intermittent and Constant Osteoarthritis Pain (ICOAP). The ICOAP assesses pain in individuals with knee osteoarthritis taking into account both constant and intermittent pain experiences (Hawker et al).

Dietary Intake. National Cancer Institute Modified Health Habits and History Questionnaire (HHHQ) provides nutrient assessment of dietary intake.

Health Literacy. Behavioral Risk Factor Surveillance System measures health literacy.

Physical Activity. The Physical Activity Scale for the Elderly (PASE) has proven reliable in many of our clinical trials, including a group of 254 men and women aged ≥65 yrs (Washburn et al).

Cognitive Functioning/Depression. The MOCA will be used to measure cognitive function (Nasreddine et al). Depression will be measured using the Center for Epidemiologic Studies Depression Scale (Burnam et al).

Inclusion/Exclusion Criteria

Inclusion Criteria:

(4) Age ≥ 50 years

(5) Knee Pain plus ACR Criteria for Knee Osteoarthritis

(6) BMI = 27 ≥ kg/m^2

Exclusion Criteria:

7. Significant co-morbid disease that would threaten safety or impair ability to participate in interventions or testing (Method: Medical history; medications; physical exam; telephone pre-screen; risk stratification)
    a. Blindness
    b. Type 1 diabetes
    c. History or symptoms of coronary artery disease or pulmonary disease with no medical clearance (symptoms include angina, unreasonable breathlessness, dizziness/fainting/blackouts)
    d. Unable to walk without a device

e. Lower extremity fracture (within previous 3 months)
f. Joint Replacement (excluded if double KR or within previous 6 months)
g. Knee injection or surgery (within previous 3 months)
h. Lower extremity injury that affects activities of daily living
i. Bariatric Surgery

8. Not sufficiently overweight or obese, BMI < 27 kg/m^2 (Method: Ht/Wt)
9. Not having knee pain: (Method: < 1 on the pain scale, WOMAC and Telephone Screen)
10. Inability to finish 18-month study or unlikely to be compliant (Method: Telephone Screen, Screening Interviews)
    a. Planning to leave area > 2 month during the next 18 months
    b. Unwilling to change eating or physical activity habits
    c. Unwilling to attend exercise/diet sessions
    d. Participating in another intervention study (only if the other study has requested they not be enrolled)
    e. Living > 30 minutes from the intervention site
11. Age, age < 50 (Method: Telephone Screen & Demographics Forms)
12. Other conditions that may prohibit the effective delivery of the intervention (Method: Telephone Screen)
    a. Unable to provide own transportation to exercise center
    b. Unable to read or write, cannot speak or read English

Randomization Procedures

We propose a stratified block randomization with block size unknown to investigators and staff will ensure equal accrual to each study arm. Prestratification will balance pretrial BMI values (27.0-34.9 kg/m^2, 35.0-44.9 kg/m^2, ≥45 kg/m^2) and gender, which could predict intervention effect and associations between secondary outcome variables. We will also use county as a fixed effect for randomization. A computer program will randomize participants into the 2 groups, verify eligibility, and provide identification number and intervention assignment. This system worked very successfully in the IDEA study.

Interventions

Diet-induced weight loss plus exercise

Months 0 -6

There will be two individual sessions per month and 2 group sessions per month for the first 6 months. The behavioral sessions will focus on awareness of changing eating habits to lower caloric intake. Educational content information regarding what food changes to make, how to make them, and why they are important will be clearly explained and discussed with participants and significant others. Each group session will include problem solving, review of a specific food topic, and tasting of several well-balanced, low-fat, nutritious foods prepared with widely available ingredients. During the individual sessions, the counselor will review individual progress, solve problems, answer questions, and set goals. During the initial individual session, the nutrition counselor will give the participant a weight history background questionnaire. The major emphasis for Period 1 is to enhance participant awareness of the importance and the need to change eating habits, i.e. lower caloric intake for weight loss. Each participant should be given the opportunity to practice skills using goal setting in a stepwise approach. Participants will follow a weekly menu plan which will incorporate meal replacements into their diet plan. Lean Shakes, a General Nutrition Center (GNC), product will be the meal replacement used. Participants may replace the Lean Shakes with a healthy, low-calorie meal of their choice, such

as Lean Cuisine. Motivation and encouragement through the combined efforts of the nutrition counselor, the participant, significant others and the nutrition staff will enhance adherence.

Months 7-12

In period 2 participants will focus on continued weight loss to reach the study weight loss goal of 10% of baseline weight. Participants will attend one group and one individual session per month. Once the weight loss goal is achieved an individual may either begin weight maintenance, or they may continue to lose additional weight using safe and healthy nutrition practices. Participants will follow a weekly menu plan with recipes using traditional foods and the option to incorporate meal replacements. The traditional meals will contain 400-600 kcals, be low in fat and added sugars, and high in vegetables, fruits, and whole grains. Snacks may be a bar, fruit, or vegetable providing ~100-120 kcals. Daily caloric intake for each participant will be adjusted to his or her rate of weight change. Each group will be encouraged to take a daily multivitamin/mineral supplement containing no more than 100% of the Dietary Reference Intake for any particular nutrient. As fewer meal replacements are consumed, intervention staff will assist in developing meal plans to provide the prescribed macronutrient-balanced energy intake.

Months 13-18

Period 3 will emphasize weight management over time, with 1 monthly individual contact. Weight loss can continue throughout the intervention, provided the participant wants to and has not reached a level associated with health hazards; i.e. a 20% body weight loss at 6 months or >30% at 12 months. Participants will continue to follow a weekly menu plan with recipes using traditional foods and the option to incorporate meal replacements.

The exercise intervention will cover an 18-month period. The exercise program will consist of a 15-minute aerobic phase, a 20-minute strength-training phase, a second 15-minute aerobic phase, and a 10-minute cool-down phase. These sixty-minute exercise sessions will be conducted three days per week (two days/week will be center based). Each participant will be prescribed an individual walking prescription by the exercise leader, which will be adjusted accordingly, as each participant progresses throughout the 18 months. The exercise will be of moderate intensity. Alternate forms of aerobic exercise, such as but not limited to stationary bike, elliptical trainer, or treadmill walking, can be used in place of over-ground walking. This choice could be based on participant preference, the limitations of the exercise facility, or the participant's pain level. To motivate participants to be physically active intervention staff will plan an optional fun walk. The walk will take place at Wake Forest University. Participants do not have to participate in the walk in order to be in the study. If a participant chooses to participate in the walk they will be asked to sign a waiver.

Intervention Locations: *Forsyth County:* The diet and exercise classes will be offered at a number of sites within Winston-Salem. Participants will be allowed to pick the location that is most convenient for them to attend. Classes will take place at the Clinical Research Center on the Wake Forest University Campus, at St. Peter's World Outreach Center, and at Smiley's Fitness. *Haywood County:* The diet and exercise classes will be held at the Haywood Regional Health & Fitness Center in Waynesville, NC. *Johnston County:* The diet and exercise classes will be held at the Clayton Community Center and the Johnston Medical Mall. Participants will also be allowed to exercise outdoors at the intervention sites when the weather permits. Staff will schedule set times when outdoor walking will be allowed.

The following measures will be taken in the event participants are unable to come into the facility:

1. Virtual Sessions - Participants will be given the option to attend virtual exercise and diet classes. Intervention classes will be taught via Zoom. Participants will be provided with the class login information. The group and diet exercise sessions will be recorded and posted to

our study Facebook page as well as sent to participants who are unable to attend the live sessions. Recordings will be edited so that only the class exercise and diet instruction can be viewed (beginning and end of the session as participants log in and out will be cut out of the video). As a security measure the virtual classes will be locked after 10 minutes so that no others can join the class. Additionally participants will not be given access to record the session. Individual sessions will also be conducted via Zoom.

2. Phone Sessions – Staff will call participants to deliver the diet group and individual session content. All participants have previously been provided with at home exercise manuals. Staff will also use this time to review our non-facility-based exercise plans.
3. Email Sessions – Participants may also choose to receive the diet group and individual session content via email. All participants have previously been provided with at home exercise manuals. Staff will also use this time to review our non-facility-based exercise plans.

All intervention staff in the WE-CAN study will be CPR certified. The exercise coordinator, who is part of the coordinating center and is responsible for maintaining exercise protocol congruity between the intervention sites, will train and supervise the intervention staff. Intervention staff will meet monthly with the exercise coordinator to discuss any potential problems, risks, and concerns that have risen. AEDs will be available at each location. Emergency drills will be performed monthly in addition the AED will be checked monthly. The clinical research center (Forsyth), Johnston Medical Mall (Johnston), and the Haywood Regional Health and Fitness Center (Haywood) also house cardiac rehabilitation programs and will also have crash carts available.

Nutrition & Health Intervention

The nutrition and health (attention control) intervention will cover an 18-month period. There will be five total face to face group meetings over the 18 months, with one meeting each at months 1, 3, 6, 9, and 15; and during the other months (months 2, 4-5, 7-8, 10-14, 16-18) participants will receive a combination of informational packets, webinars, text messages, and emails. Participants will be able to select their preferred method. Each group meeting will last approximately one hour and will be held at St. Peter's World Outreach Center and at Senior Services in Winston-Salem, NC. The sessions will be interactive and will provide useful information on such topics as proper foot care, general nutrition, health behaviors, management of medications, and sleep practices. The Community Advisory Board will give input on the class sessions.

Experts across a broad range of relevant topics that are of interest to older adults will provide information via information packets, webinars, text messages or emails. These monthly contacts and email blasts will keep the participants in the nutrition and health group engaged in the WE-CAN study and will increase adherence to the group sessions and the testing visits.

Participants in both interventions will be provided with items with the study logo such as t-shirts and tote bags to promote group bonding and study adherence. Additionally, giftcards will be raffled at various class sessions. In order to better balance the amount of money spent on the two groups participants in the Nutrition & Health group will receive a $100 (gift cards) for completing the testing appointments. They will be given $25 at 6 months and $75 at 18 months. At the 12-month testing appointments the participants will receive an incentive with the study logo. Participants in the Diet & Exercise group will be receiving meal replacements for the first year of the study.

995 Procedures-Screening and Follow-up Visits.

Measurements	PSV	SV1	FU6	FU12	FU18	Explanation
Questionnaires						
Informed Consent		x				
Eligibility Questionnaire	x					To determine eligibility
Medical History/Med History FU	xc	x	x	x	x	For eligibility and to document changes in health
Risk Stratification	xc	x				Used to screen cardiovascular risk
Comorbidities Questionnaire		x		x	x	
Randomization		x				
WOMAC		x	x	x	x	Pain is primary and function secondary outcomes. Will be taken from the KOOS
Knee Injury and Osteoarthritis Outcome Score (KOOS)		x	x	x	x	Assesses patient's opinion about their knee and associated problems
PASE scale		x	x	x	x	Physical Activity Scale for the Elderly
MOCA		x			x	Montreal Cognitive Assessment
EuroQol Quality of Life(EQ5D)		x	x	x	x	Quality of life measure
Resource Utilization		x	x	x	x	Visits to clinicians, tests, medications, injections, surgery, alternative therapies
Work Productivity and Activity Impairment Index		x	x	x	x	assesses absenteeism and presenteeism
DHQ II		x	x	x	x	NIH Diet History Questionnaire
SF-36		x	x	x	x	Health related quality of life (physical, mental)
Health Literacy		x	x	x	x	
Adherence Self Efficacy		x	x	x	x	Confidence in exercising at various intensities and frequencies
Adherence for Duration		x	x	x	x	Confidence in walking for different durations
Gait Efficacy		x	x	x	x	Confidence in completing tasks
Demographics		x				
Medication form		x	x	x	x	Atherosclerosis Risk in Communities form
Weight Efficacy Questionnaire		x	x	x	x	Self-Efficacy for Weight Management
PANAS		x	x	x	x	Positive and Negative Affect Scale
SWL		x	x	x	x	Satisfaction with Life
Perceived Stress		x	x	x	x	Stress
Pain Catastrophizing Scale		x	x	x	x	Catastrophizing
Intermittent and Constant Osteoarthritis Pain (ICOAP)		x	x	x	X	Intermittent and Constant Pain
CES-D		x	x	x	X	Depression
Transition Questionnaire			x	x	X	Knee pain
Adverse Events			x	x	X	Also collected as they occur
Physical Performance Tests/Knee Exam						
height	xc	x				To determine BMI
weight	xc	x	x	x	X	To determine BMI
Knee exam		x				To determine eligibility
6 minute walk		x	x		X	Measure of mobility
Expanded Short Physical Performance Battery (SPPB)		x	x	x	X	Gait speed, sit to stand, balance tests; predicts disability
GaitRite		x	x	x	X	mobility measures
Stair Climb		x	x	x	X	mobility measure
xc = brief screen by self-report, PSV = Prescreening Visit. SV = screening visit. FU = follow-up.						

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997 Procedures-Screening and Follow-up Visits.

998 Prescreening visit (PSV). Individuals who contact our recruitment office in response to advertising will be
999 asked a series of brief questions that focus on major eligibility criteria. A screening visit appointment will be
000 made for participants who meet major eligibility criteria. A medical history form and a medication form will
001 be mailed to the participants for them to complete. If participants are unable to come in for testing
002 appointments research staff will call participants via Webex to collect study data (participants can choose
003 whether to attend virtually or only via phone). Staff will use a HIPPA compliant version of Webex (set up by
004 Wake Forest University). To reduce participant burden only the following questionnaires will be collected:
005 cost effectiveness questionnaires, WOMAC, KOOS, Physical Activity Scale for the Elderly (PASE), Health-
006 Related Quality of Life (HRQL), and efficacy measures. In the event participants do not wish to conduct a
007 phone or virtual session a questionnaire packet will be mailed to participants to complete and return. The
008 webex testing session will last approximately 1 hour.

Screening Visit One (SV1) Individuals will come to Worrell Professional Building on the campus at Wake Forest University. SV1 includes an explanation of the study and obtaining informed consent. Other assessments include medical history and medication use (previously mailed), cardiovascular risk, height and weight (to calculate BMI), hip/waist circumference measurements, blood pressure, and a knee exam. The MOCA & CES-D will be administered. The following questionnaires will be given: demographics, cost effectiveness questionnaires, WOMAC, KOOS, Physical Activity Scale for the Elderly (PASE), Health-Related Quality of Life (HRQL), dietary intake questionnaires, health literacy, perceived stress, pain catastrophizing, and efficacy measures. Physical performance measures include the SPPB, 6 minute walk, GaitRite, and stair climb. This screening visit will last approximately 3 - 4 hours.

Randomization Visit (RV) Individuals will come to Worrell Professional Building on the campus at Wake Forest University. At the RV an orientation to the group will be done.

6-month Follow-up Data Collection Visit (FU6): Participants will return to Worrell Professional Building to repeat all measures collected at baseline (minus the MOCA, knee exam, and demographics). The testing session will last approximately 2.5 – 3.5 hours.

12-month Follow-up Data Collection Visit (FU12): Participants will return to Worrell Professional Building to repeat all measures collected at baseline (minus the knee exam and demographics). The testing session will last approximately 2.5 – 3.5 hours.

18-month Follow-up Data Collection Visit (FU18): Participants will return to Worrell Professional Building to repeat all measures collected at baseline (minus the knee exam and demographics). The testing session will last approximately 2.5 – 3.5 hours. At the end of 18 months the participants will have a mini session on what the other group received.

Usage of Facebook

The research study would like to incorporate the usage of Facebook in the study. We plan on using Facebook in the following ways.

1) Recruitment
    a. The study has created digital ads (submitted with this amendment) that will be used in Facebook ads. Ads posted will be pop up ads.

2) Study Notifications & Contact Method
    a. The study will set up a Facebook page in which participants will be given the link (usage will not be required but will be an additional method that participants can use to contact study staff or find out study information). A description of this usage is listed below.
        i. Study info such as press releases, news articles, manuscripts will be posted to the study Facebook page. This information will also be provided in study newsletters (for those not on Facebook).
        ii. Information regarding site closings (such as in the event of inclement weather or holidays) or intervention materials (group intervention classes) will be posted on the Facebook page. Please note all participants will be given information regarding holiday closings and weather policies in their intervention classes. A study phone number will be given to each participant which will be updated in the event of a closing. It will not be necessary to check Facebook to learn of a study closing.

iii. Participants in the study will also be able to use Facebook as a means of contacting the staff by sending a private message (email) to the staff. This method may be useful to the nutrition and health group in which participants will be given a choice to their preferred method of contact (email, phone, Facebook private message).

3) Participant Posting
   a. The study will set up its account as a page therefore it will not be a private group. Therefore the study will only post study information (press releases, articles, etc.) and site information. We will not post pictures or study participant information. However participants whom are on Facebook will be allowed to post to the study page. All posts will be reviewed by the study staff to ensure no other participants are identified as being a part of the study.

Informed Consent

Signed informed consent will be obtained from each subject. Consent will be obtained by study coordinator, interventionists, and testing staff. Participants will be consented at screening visit one (SV1). Upon arrival each potential subject will meet with a staff member to review the study consent form. No study specific procedures will be done prior to the signing of the consent form. Staff members administering the informed consent must use the following steps in order to orient the potential subject to the purpose of the research.

- The staff member will verbally explain the study to the potential subject, providing all pertinent information (purpose, procedures, risks, etc.), and will allow the potential subject ample opportunity to ask questions.
- Following this verbal explanation, the potential subject will be provided with the consent form and schedule to review. The potential subject will be given as much time as they need to consider whether or not to participate in the research.
- After allowing time for the potential subject to read the consent form, the staff member, will meet with the potential subject to answer any additional questions he/she may have.
- Once the potential subject has all of their questions answered and has agreed to participate, they will be asked to sign and date the consent form. The staff member will also sign and date the consent.
- A copy of the informed consent will be made and given to the subject.

In the event a person wishes to discuss the study with a family member or would like additional time to think about participating in the study, the staff member will make a note of this in the subject file and the staff will follow-up with the potential subject.

Once a person has completed the screening appointment and the data has been entered into study website the project manager will randomize the subject by selecting the randomization program in the WE-CAN website. Participants will be placed into either the diet & exercise group or the attention control (nutrition & health) group.

Safety Monitoring Plan

An internal safety committee has been established to monitor participant safety and to evaluate the progress of the study. In addition NIAMS has selected a DSMB to monitor study safety and progress.

Adverse Event and Serious Adverse Event Collection and Reporting

Adverse Event (AE) - An AE is any unfavorable and unintended diagnosis, sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the study intervention, which may or may not be related to the intervention, including excessive delayed onset muscle soreness (DOMS) as some minimal muscle soreness will be expected after the training session. AEs include any new events not present during the pre-intervention period or events that were present during the pre-intervention period which has increased in severity. Participants will be asked if any events have occurred on a monthly basis prior to their intervention class and at each testing session. Participants will be encouraged to report AEs as they occur.

Study staff will report non-serious adverse events (related and unrelated to the study) to site project manager and principal investigator within 7 days of notification of the event and will be reported to the coordinating center quarterly. Testing staff will inquire about adverse events prior to testing to ensure there are no unreported events. The site physician/PA will review non serious adverse events (AE) on a weekly basis. Non serious adverse events will be included in the NIAMS safety report and submitted bi-annually.

Serious Adverse Event (SAE) - An SAE is any untoward medical occurrence that results in death, is life-threatening, requires or prolongs hospitalization, causes persistent or significant disability/incapacity, results in congenital anomalies/birth defects, or, in the opinion of the investigators, represents other significant hazards or potentially serious harm to research participants or others.

Staff will report serious adverse events (related and unrelated to the intervention) to the site project manager, principal investigator, and study physician. The clinical site will reports SAEs to the coordinating center within 24 hrs of notification. SAEs will be reported to NIAMS within 24 hours of being reported to the PI (within 48 hours of initial report). The WFU IRB does not require the reporting of adverse events unless it is serious, unexpected and related to the study. Follow-up information will be provided to the PI, DSMB/Safety Officer, and IRB, as appropriate.

NIAMS has assigned a Data Safety Monitoring Board (DSMB) or safety monitor to monitor all aspects of the study.

The DSMB/Safety Monitor will have the following charges:

- To review the entire study protocol, the operations manual, and the informed consent and assent forms for recruitment, randomization, intervention, participant safety, data management, auditing plans for participant records, and quality control and analysis plans, and to identify needed modifications.
- To review data related to efficacy, recruitment, randomization, compliance, retention, protocol adherence, trial operating procedures, forms completion, intervention effects, gender and minority inclusion, and participant safety over the course of the trial.
- To identify problems related to safety over the course of the study and to report them in writing to the PIs, who will ensure that the appropriate individuals receive the report.
- To identify a need for additional data relevant to safety and to request them from investigators.
- To propose appropriate analyses and periodically review developing data on safety and endpoints.
- To make recommendations regarding recruitment, intervention effects, retention, compliance, safety, and continuation of the study.
- To send the Program Administrator and PIs written reports following each DSMB meeting, addressing all issues raised, and subsequently sent to the IRB.
- At any time, the DSMB may recommend discontinuation of any component/intervention of the study for any of the following reasons:

1) Compelling evidence from this or any other study of an adverse effect sufficient to override any potential benefit of the interventions to the target population.
2) Compelling evidence from this or any other study of a significant beneficial effect whose continued denial to other study group(s) would be unethical.
3) A very low probability of addressing the study hypothesis within a feasible time frame.

Statistical Considerations

Data Management

The Data Management Group, part of the Coordinating Center, has primary responsibility for randomization and analyzing data generated by the clinical centers. Data will be collected on hard-copy forms at each site and transformed to an electronic database. Our web-based management system will assure integrity and validity. Dynamic reports and periodic statistical analyses will monitor quality. A participant-based inventory system will track recruitment, retention, adherence, and missing data from entry through exit, close-out, and lock-down of final datasets. Our team developed a similar database for the IDEA and START studies.

Statistical Analyses

Statistical analyses will be conducted according to intention-to-treat principles using SAS.

Primary Aim.

The primary hypothesis of long-term reduced WOMAC pain at 18 months will be tested based on a two-tailed significance level of 0.05 using contrast statements from a repeated measures mixed linear model with time (6, 18 mos), randomization arm (D+E vs control), and the interaction, which adjusts the means at each time point for potential missing data bias (Laird and Ware). Intervention-effect estimates will be further adjusted for baseline pain values, BMI, county, and gender; analysis will match design, so the variance estimate will not be biased. Participant ID number will be included as a random effect to control for within-subject variability, and the longitudinal model will use an unstructured covariance matrix. In the unlikely event the model does not converge, a first-order autoregressive (AR[1]) covariance structure will be fit instead. Maximum-likelihood techniques will estimate parameters, as in the IDEA trial (Messier et al). Preliminary analyses will be conducted to check the shape of the distributions and variances between groups and as a function of the covariates. Regression diagnostics and residual plots will help to find appropriate transformations, if necessary. We will include exploratory analyses of subgroups, defined by gender, age (<70 vs ≥70 years), baseline BMI (27.0-34.9, 35-44.9, ≥45 kg/m^2), county, and race to determine any differential pain responses.

Secondary Aims

Repeated measures mixed linear models similar to Aim 1 will be used to analyze WOMAC function, 6-minute walk, and SF-36 physical subscale. Each outcome will be modeled separately, and 18-month effectiveness will be tested based on a two-tailed significance level of 0.05. The model will include the fixed effects study arm, time, time-group interaction, county, gender, baseline BMI, and baseline values of the outcome; participant ID number will be included as a random effect, and an unstructured covariance will be used assuming model convergence is not a problem (AR[1] otherwise). Preliminary analyses will be conducted to check the shape of the distributions and variances between groups and as a function of the covariates. Regression diagnostics and residual plots will help to find appropriate transformations, if necessary.

Missing Data

If missing data are related to outcomes, our results could be biased. Our models will include variables from previous visits determined to predict loss to satisfy Little and Rubin's conditions for data considered missing at random (MAR). If "informative censoring" occurs, we will compare analyses using subjects with complete data, multiple imputations, or explicit modeling of the censoring mechanism (Conaway, 1993, Wu and Bailey, 1989).

Primary Outcomes

Aim 1. A total sample of 820 (410/group) will provide 94% statistical power to detect differences ≥15% in pain at the 2-sided 0.05 significance level with 80% retention (2-sample t-test, Nquery Advisor). Based on ADAPT (Messier et al). The D+E group in IDEA reduced pain by an average of 51%. This approach utilizes the conditional variance approach of Borm et al. for the estimation of power for ANCOVA models using group standard deviation $\sigma = 3.50$, Pearson correlation between baseline and 18-month pain score of $\rho = 0.4$ for a conditional standard deviation $\sigma_c = 3.21$ ($\sigma_c = \sqrt{1-\rho^2} \times \sigma$), and 18-month treatment WOMAC pain means ~D+E = 5.03 vs E-only control = 5.92 (Δ = -0.887). Variations of anticipated power due to modifications in retention and treatment effect are presented in Table 1. Correlation between baseline and 18 month pain values are estimated from the IDEA trial, while anticipated treatment effects and standard deviation for pain were obtained using weighted averages of D+E and non-D+E treatments from the ADAPT and IDEA studies, with some attenuation of the anticipated treatment effect due to the pragmatic nature of WE-CAN (Table 1).

Table 2: Detectable absolute and relative (%) differences for secondary outcomes, n = 410/group, 80% retention, 85% statistical power, α = 0.05. Correlation between baseline and 18M values is ρ.

Variable	Anticipated 18m Control mean*	Standard Deviation	ρ	D+E Mean (% change from C)
WOMAC Function	17.5	11.5	0.6	15.3 (-12.3%)
Mobility: 6-Minute Walk (m)	509	90.7	0.7	524 (3.0%)
SF-36 Physical Score (0-100)	42.0	10.1	0.5	44.1 (4.9%)

Table 1: Power estimates for WOMAC pain, assuming baseline N=820, correlation between BL and 18 months=0.4, and common group SD = 3.50.

18 month Control Mean WOMAC Pain	18 Month D+E WOMAC Pain (% difference from Control)	18-Month Retention			
		70%	75%	80%	85%
		Power			
5.92	5.15 (13%)	81%	84%	86%	88%
	5.03 (15%)	91%	92%	94%	95%
	4.91 (17%)	96%	97%	97%	98%

Secondary Outcomes

Aim 2. Our sample size provides a moderate effect size of 0.234 at 85% power with relevant detectable differences. However, all estimates from IDEA and ADAPT were collected under rigorously controlled conditions; therefore the estimates for the pragmatic trial are conservative. We assume in Table 8 a total baseline sample size of N=820, 80% retention at 18 months, and a 0.05 level of significance for all tests. The detectable and % differences from control aim to achieve 85% power. The mean differences in WOMAC function for D+E compared to D only and E only in IDEA were -3.3 and -4.3, respectively. Likewise, the differences in 6-minute walk distance for the D+E group versus D only in IDEA and ADAPT (41.5 and 42.1, respectively) indicate that the mean difference to achieve 85% power (15.2 m) is modest. IDEA indicated that SF-36 physical subscale was significantly improved in the D+E arm, with an observed difference of 2.8 compared to E alone (Table 2).

Clinical Protocol Synopsis

Weight loss and Exercise for Communities with Arthritis in North Carolina (WE-CAN)

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National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)

16. Clinical Protocol Synopsis

The clinical protocol is detailed in the Research Plan, Appendices, and the Manual of Operations (Appendix G). Below is a synopsis of these procedures.

Trial Organization

The organizational structure, committees, and committee meeting schedules are detailed in Appendix C and in the Manual of Operations (Appendix G). Briefly, there will be three intervention centers, Forsyth, Johnston, and Haywood counties in North Carolina and a Coordinating Center at Wake Forest Health Sciences in Forsyth County. The intervention will be delivered at 3 sites in Forsyth County, 2 sites in Johnston County, and 1 site in Haywood County. The Coordinating Center, which includes the Data Management group, oversees the day-to-day operation of the trial including heading recruitment, randomization, analyzing data, organizing training sessions, coordinating central resources, providing reports to the DSMB, and collaborating for manuscript preparation describing trial results. The Executive Committee (PIs, site PIs, ad hoc member), with input from the co-investigators, is responsible for major policy decisions that govern the conduct of the trial.

Description of study population:

Participants will be 820 ambulatory, community-dwelling, overweight and obese (BMI ≥ 27 kg/m^2) men and women aged ≥ 50 yrs who meet the American College of Rheumatology clinical criteria for knee OA, which includes knee pain on most days of the week plus at least 3 of the following 6: age ≥ 50 years; stiffness < 30 min/day; crepitus, bony tenderness; bony enlargement; no palpable warmth.

Sampling, recruitment, and enrollment plans.

Recruitment goals for each county were based on previous recruitment successes and population densities; Forsyth, Johnston and Haywood Counties' recruitment goals are 450, 220, and 150, respectively (total = 820). We exceeded our goals in Forsyth County for FAST (209 randomized with a goal of 200), ADAPT (316 with a goal of 300), and IDEA (454 with a goal of 450); in Johnston County we have a history of successful recruitment for a range of intervention studies (see preliminary studies); in Haywood County Dr. Queen has successfully recruited participants for collaborative studies with Drs. Jordan and Callahan (e.g. 23 randomized in 30 days). Yields (number randomized/number of inquiries) were 10%, 14%, and 15%, for FAST, ADAPT, and IDEA, respectively. With fewer exclusion criteria in WE-CAN, we conservatively estimate an average yield of 15%. A web-based data tracking system will monitor recruitment strategies in each county.

We use overlapping recruitment strategies and a monitoring system that provides feedback regarding the effectiveness and cost of each. Forsyth County will use mailings, local newspaper ads, and Wake ONE, the Wake Forest Baptist Hospital patient database. We also have strong ties with local aging service networks and access to senior centers, senior high-rise residential sites, churches, and a large database of older adults who have signed consent to be contacted about participating in future clinical trials. UNC has a similar relationship with Johnston County, where Dr. Jordan has ready access to a large segment of the population, many who have signed consent to be contacted for future studies. The most successful recruitment methods for clinical trials in the county have been through the Johnston County Health System, primary care offices, local newspapers, the Seniors Guide, a Parks and Recreation Brochure, the newsletter for the Town of Clayton, and the Clayton Community Center. Dr. Queen and Drs. Jordan and Callahan have collaborated on several trials. Methods of recruitment in Haywood include community talks, Dr. Queen's practice (12 physicians), newspaper ads, local orthopedic groups, MedWest Fitness Center, and the Outpatient Rehab Center.

Process for obtaining informed consent.

Upon arrival each potential subject will meet with a staff member to review the study consent form. No study specific procedures will be done prior to the signing of the consent form. Staff members administering the

informed consent must use the following steps in order to orient the potential subject to the purpose of the research.

- The staff member will verbally explain the study to the potential subject, providing all pertinent information (purpose, procedures, risks, benefits, alternatives to participation, etc.), and will allow the potential subject ample opportunity to ask questions. The following points will be covered.
    - *Study Purpose:* We are studying the effects of weight loss and exercise on arthritis symptoms.
    - *Study Description*: There will be two equal groups, one group will attend 2 group and 2 individual sessions per month in the first 6 months, followed by a monthly group and individual session for the following 6 months, and lastly monthly group classes for the remaining 6 months. In addition you will attend an exercise class 2x/week. You will be asked to exercise at home 1x/week. The attention control group will attend successful aging classes and will perform stretching exercises. They will meet 4 times over the course of the study and will receive informational packets, webinars, texts, and emails for each of the other months. At the start of the study they will be asked to select their preferred mode of contact (phone, email, study website, or text messages), and information will be distributed accordingly. The tests involved with the study include a physical exam, walking and strength tests, and questionnaires.
    - *Risks:* There are some risks associated with the study including: muscle/joint soreness or falling during the walking and strength training; and breach of personal information. The study staff will take the following measures to minimize these risks: testing areas will be reviewed prior to testing/training to ensure there are no obstacles in the way that may cause a trip/fall; participants will be trained on proper strength training and stretching techniques; and all records will be kept in secure locations in which only authorized persons will have access.
    - *Benefits:* Researchers believe that exercise and weight loss are important in relieving the symptoms of OA; however, because people respond differently, no one can know in advance if it will help in your particular case.
    - *Alternatives:* You do not have to participate to receive treatment. You do have the option of being treated with conventional medical therapy or participate in a community lifestyle program.
- Following this verbal explanation, the potential subject will be provided with a written consent form to review. The potential subject will be given as much time as needed to consider whether or not to participate in the research.
- After allowing time for the potential subject to read the consent form, the staff member, will meet with the potential subject to answer any additional questions s/he may have.
- The staff member will also ask the potential subject questions to ensure the potential subject understands the study (including purpose, risks, benefits, and alternatives) and does not have any additional questions.

Approaches used for retention, cooperation, and follow-up.

WE-CAN's design evolved from Social Cognitive Theory (SCT), group dynamics, and over two decades of weight management and exercise trial experience. Our 18-month FAST, ADAPT, and IDEA trials had 80%-88% retention (i.e., returned for final testing visit) and 64-70% adherence (i.e., attendance to exercise and weight loss classes).

Drs. Mihalko and Callahan will train WE-CAN community interventionists in standardized and validated behavioral techniques based on a SCT framework to enhance adherence. They include regular contact during the intervention; positive feedback; establishing personal commitment to the project; promoting a sense of community via study logo, cards, and newsletters; and developing self-efficacy, outcome expectations, and self-regulatory skills. From the outset, the importance of regular attendance will be emphasized and data will be reviewed regularly to identify those who need additional reminders and/or counseling.

Our toolbox approach tailors the intervention to participant needs. Each strategy identifies a problem and tests a solution for a specific period. If the problem is resolved, the strategy is continued until behavior change is consistent. If not, a new strategy is selected and tested for a specific period. Some can be used in groups, while others require one-on-one interaction via telephone or face-to-face meeting. For example, if a participant

misses 2 consecutive sessions and has had no contact with the interventionist, a phone session will be scheduled. The interventionist will assess the participant's study goals, time management, care-giving concerns, and feelings of connectedness to group objectives. Together, they will develop a specific plan. Adherence rates will be regularly reviewed with the Adherence and Retention Committee. Site-specific adherence rates and barriers to participation will be discussed and strategies to promote adherence reviewed. *Our team has had remarkable success with this tiered approach; adherence and retention rates have exceeded study goals on numerous federally funded projects examining weight loss and exercise interventions.*

A description and justification for selection of the dose, frequency, and administration of the intervention.

The weight loss goal of the D+E group is a minimum of 10% of baseline body weight, as recommended by the National Institutes of Health for overweight and obese adults and is consistent with our results in IDEA (1) in which an 11.4% weight loss, when combined with exercise, reduced knee pain by 51%. The attention control (C) group is modeled after our previous studies' attention control groups, providing attention, social interaction, and health education (2, 27) The dietary plan is characterized by the frequency of contacts, methods to induce dietary restriction, and behavioral therapy strategies. For the first 6 months, the plan will be based on an energy-restricted diet using 1 to 2 partial meal replacements (GNC®) per day with options to incorporate 1 meal replacement per day during months 7-18. The plan will be individualized and based on the highly successful program used in IDEA. Based on IDEA, most participants will reach their weight loss goal after 9 months. Once the weight loss goal is achieved an individual may either begin weight maintenance, or may continue to lose additional weight using safe and healthy nutrition practices.

The exercise component of the D+E intervention will include 60-minute sessions 3 days per week (d/wk) for 18 months. During the first 4 months, participants will exercise 2 d/wk at one of the designated community facilities and 1 d/wk on their own (at home or community facility). Any time afterward, those wishing to exercise on their own every day will alternate between the facility and on their own during a 2-month transition phase. Based on IDEA, we expect most will choose to maintain the combination of facility and home based exercise. The exercise program prescribed to each participant will consist of aerobic (15 min), resistance-training (20 min), a second aerobic (15 min), and cool-down (10 min) phases. Strength training is particularly relevant to offset any loss of muscle and bone mass resulting from weight loss. In addition to the 3 scheduled days, participants will be encouraged to exercise most other days of the week on their own. This protocol is consistent with the American College of Sports Medicine guidelines for exercise for older adults (38). Monthly exercise logs will be used to monitor progress.

A description of the each enrollment site and how data from each site will be obtained, managed, and protected.

Clinical Centers will be established in Forsyth (3 intervention sites), Johnston (2 intervention sites), and Haywood (1 intervention site) Counties. Each clinical center consists of a team of investigators and staff who provide the areas of expertise necessary for the successful completion of the WE-CAN protocol. Each center will have a Site-PI, a Site-Project Manager, a research technician, and two community interventionists that will be crossed trained to lead the nutrition classes, the exercise classes, and organize and run the attention control group. These personnel will provide the expertise necessary for the successful completion of the protocol. Clinical Center site responsibilities include:

1. Recruiting participants for the trial;
2. Confirming eligibility of all participants;
3. Implementing the interventions in a systematic and standardized fashion consistent with the study protocol;
4. Making provisions to ensure the safety of trial participants;
5. Collection of data according to the study protocol;
6. Entering and uploading data to study database;

7. Collaborating in design and monitoring of the study;
8. Collaborating in the analysis and dissemination of study results;

The Data Management Group, part of the Coordinating Center, has primary responsibility for randomization and analyzing data generated by the clinical centers. Data will be collected on hard-copy forms at each site and transferred to an electronic database. Our web-based management system will assure integrity and validity. Dynamic reports and periodic statistical analyses will monitor quality. A participant-based inventory system will track recruitment, retention, adherence, and missing data from entry through exit, close-out, and lock-down of final datasets. Our team developed a similar database for the IDEA and START studies.

Confidentiality of enrolled person's data will be protected. Data will be maintained in locked file cabinets and on password protected computer files. Data will only be accessible by the PI and his/her staff at the intervention site, and by those who are providing services for this research project or are responsible for overseeing research (i.e. WFUHS statisticians, IRB).

A description of all clinical and behavioral tests to enable the research question to be answered.

The Likert version of the Western Ontario McMasters Universities Osteoarthritis Index (WOMAC) will be used to measure **pain (primary outcome)** on a scale from 0 (none) to 4 (extreme). The pain subscale consists of 5 items, and total scores range from 0-20; higher scores indicate greater dysfunction. The Osteoarthritis Research Society International supports the validity of this instrument and recommends it as the health status measure of choice in older adults with knee OA. The **WOMAC function subscale** is also 0-4 and queries the degree of difficulty experienced in the last 48 hours due to knee OA. Individual scores for the 17 items are totaled to generate a summary score from 0-68; higher scores indicate poorer function (39). Other secondary measures are noted in the table below.

Table. Measurements with screening and follow-up visit schedule

Measurements	PSV	SV1	FU6	FU12	FU18	Explanation
Questionnaires						
Informed Consent		x				
Eligibility Questionnaire	x					To determine eligibility
Medical History	xc	x	x	x	x	For eligibility and to document changes in health
Comorbidities Questionnaire		x	x	x	x	(40)
Randomization		x				
WOMAC		x	x	x	x	Pain is primary and function secondary outcomes
Cost Effectiveness		x	x	x	x	See section c.4.9. for details
PASE scale		x	x	x	x	Physical Activity Scale for the Elderly (28, 41)
MOCA		x			x	Montreal Cognitive Assessment, (42, 43)
EuroQol Quality of Life(EQ5D)		x	x	x	x	Quality of life measure (44)
Work History Resource		x	x	x	x	Visits to clinicians, tests, medications, injections, surgery, alternative therapies
Work Productivity and Activity Impairment Index		x	x	x	x	assesses absenteeism and presenteeism (45)
DHQ II		x	x	x	x	NIH Diet History Questionnaire (36, 37)
SF-36		x	x	x	x	Health related quality of life (physical, mental) (46)
Self-Efficacy-Adherence		x	x	x	x	Belief can exercise at various intensities (47)
Demographics		x				
Medication form		x	x	x	x	Atherosclerosis Risk in Communities form (48)
Adverse Events			x	x	x	Also collected as they occur
Physical Performance Tests/Knee Exam						
Height	xc	x				To determine BMI
Weight	xc	x	x	x	x	To determine BMI
Knee exam		x				To determine eligibility
6 minute walk		x	x	x	x	Measure of mobility (49)
Short Physical Performance Battery (SPPB)		x	x	x	x	Gait speed, sit to stand, balance tests; predicts disability (50)
Functional Leg Strength		x	x	x	x	Sit to stand test, part of SPPB

xc = brief screen by self-report, PSV = Prescreening Visit. SV = screening visit. FU = follow-up.

Provide evidence of the ability of each center to enroll the proposed numbers, adhere to the protocol, collect and transmit data, and operate within the organizational structure.

Recruitment goals for each county were based on previous recruitment successes and population densities; Forsyth, Johnston and Haywood Counties' recruitment goals are 450, 220, and 150, respectively (total = 820). We exceeded our goals in Forsyth County for FAST (209 randomized with a goal of 200), ADAPT (316 with a goal of 300), and IDEA (454 with a goal of 450); in Johnston County we have a history of successful recruitment for a range of intervention studies (see preliminary studies); in Haywood County Dr. Queen has successfully recruited participants for collaborative studies with Drs. Jordan and Callahan (e.g. 23 randomized in 30 days). Yields (number randomized/number of inquiries) were 10%, 14%, and 15%, for FAST, ADAPT, and IDEA, respectively. With fewer exclusion criteria in WE-CAN, we conservatively estimate an average yield of 15%. A web-based data tracking system will monitor recruitment strategies in each county.

A number of strategies are used to enhance adherence. They include regular contact during the intervention; positive feedback; establishing personal commitment to the project; promoting a sense of community via study logo, cards, and newsletters; and developing self-efficacy, outcome expectations, and self-regulatory skills. From the outset, the importance of regular attendance will be emphasized and data will be reviewed regularly to identify those who need additional reminders and/or counseling.

Our toolbox approach tailors the intervention to participant needs. Each strategy identifies a problem and tests a solution for a specific period. If the problem is resolved, the strategy is continued until behavior change is consistent. If not, a new strategy is selected and tested for a specific period. Some can be used in groups, while others require one-on-one interaction via telephone or face-to-face meeting. For example, if a participant misses 2 consecutive sessions and has had no contact with the interventionist, a phone session will be scheduled. The interventionist will assess the participant's study goals, time management, care-giving concerns, and feelings of connectedness to group objectives. Together, they will develop a specific plan. Adherence rates will be regularly reviewed with the Adherence and Retention Committee. Site-specific adherence rates and barriers to participation will be discussed and strategies to promote adherence reviewed. *Our team has had remarkable success with this tiered approach; adherence and retention rates have exceeded study goals on numerous federally funded projects examining weight loss and exercise interventions.*

Adherence to scheduled testing visits, exercise sessions, and nutrition classes (both face-to-face and by other means) will all be monitored by the Coordinating Center staff. Attendance data will be uploaded to an electronic database monitored by the Data Management Group of the Coordinating Center. Coordinating Center staff will review, at regular 2-week intervals, recent participant attendance and completeness of data collection at each site. These reports will be submitted to the Data and Safety Monitoring Board.

Training Study Personnel.

Coordinating Center personnel will provide **on-site training** for the community interventionists during the 6-month planning period (and during the course of the trial for newly hired leaders) and tailor the instruction to the local facilities. For example, some exercise facilities will have indoor tracks conducive to walking, while others with less space may use treadmills, elliptical trainers, or low-impact aerobic dance. Some facilities may have a full kitchen for nutrition classes, while others may have no kitchen facilities in meeting rooms. **Tailoring the intervention to each facility and employing and training people from the local community supports our pragmatic study design.** Following the initial training sessions, the Coordinating Center's interventionist team will monitor the progress of each site via bi-weekly WebEx meetings with our psychologist, examining adherence rates and barriers to participation, noncompliant participants, and strategies that have proved successful. These core values are consistent, effective mediators for translating knowledge into practice.

Demonstration of availability of study agents.

We have entered into an agreement with Dr. Guru Ramanathan, Chief Innovation Officer at GNC, to supply the meal replacements at a reduced cost (see letter of support). We have a long history of working with Dr. Ramanathan and GNC as suppliers of the same meal replacement product used for IDEA.

Quality Management Plan

1.A. Standard Operating Procedures (SOPs)

The Coordinating Center will be responsible for the distribution and training of SOPs. The date research staff has been trained will be documented. Research staff will be monitored consistently and receive refresher training at regular intervals to ensure compliance. SOPs will be reviewed annually to reassess applicability.

1.B. Data and Form Checks

Once the subject is finished completing the forms, the forms will be checked for accuracy. The tester will check to see if each question has been completed correctly such as no double responses, dates are correct (for example birth year is entered vs. current date), etc. The tester will also ensure that there are no skipped responses or missed pages. If a response(s) or page is empty the tester will have the subject complete that question(s) or page. If an error (such as date seems incorrect) is found the tester will ask the subject to verify the response and if incorrect the subject should put a line through the incorrect response and initial next to it and then write in the correct response.

All forms should be completed in their entirety. If a form cannot be completed the tester should write the reason as to why the form couldn't be completed (such as participant refused to answer question) and should initial and date next to the missing item.

All persons will be trained on how to access the website and on how to enter forms. New users will undergo a training period in which they will be given duplicate paper forms to enter into the website on separate occasions. The error rate will be calculated and if not acceptable (error rate must be ≤ .05%) the user will repeat the process until the error rate is deemed acceptable. In addition, if a user's error rate was previously deemed acceptable and becomes unacceptable at a later period they will be retrained and will have to repeat the training process.

1.C. Double Data Entry

Paper forms will be entered into 2 separate data bases and compared. Error reports displaying conflicting entries will be given to the project manager who will have the research technician pull the paper form to verify the correct response and edit the record within the website.

Edits are performed by retrieving the current record for editing in the same web form in which it was submitted. Upon resubmission, all of the current validation rules and message are reapplied to the edited data as describe above for the original entry.

1.D. Clinical Monitoring

Regular site visits will be scheduled for all clinical centers regardless of performance, to ensure that developing problems are detected early, that activities are consistent across centers, and that successful implementation strategies are shared. Clinic staff will receive central training, and re-training in the study protocol. Site monitoring will take place through semi-annual site visits conducted by the coordinating center. The coordinating center will perform an initiation visit prior to the recruitment of subjects to assist with training, periodic monitoring visits (to ensure sites are maintaining the and following the study protocol), and a close out visit.

1.D.1. Initial Visit

During the site initial visit the clinical center study team will receive adequate training from the Coordinating Center. This visit will occur after the site has completed all regulatory requirements and has obtained IRB approval for the research study at their site.

Other topics of discussion during the site initiation visit include:

- Study overview, eligibility criteria, procedures, and recruitment
- Review of SOPs (examples include: Informed consent requirements, IRB obligations, adverse event reporting)
- Data forms review

- Regulatory documents and study file organization

1.D.2. Periodic Monitoring Visits

The administrative group of the coordinating center staff will perform semi-annual monitoring visits. The focus of these visits is to evaluate the way the study is being conducted and to perform source document verification. Documents will be verified to ensure:

- Informed consent has been obtained and documented in accordance with IRB regulations
- All information recorded on the forms is complete and accurate or if missing is noted.
- That all Adverse Event (AE) and Serious Adverse Event (SAE) forms have been submitted

Once the site visit is complete, feed- back will be provided to the site project manager and site PI for any issues that may have been discovered during the visit. The site will be given a timeline in which the issues should be corrected and reported back to the coordinating center.

1.D.3. Close-Out Visit

Once the study has ended a close-out visit will be performed. Action items during the close-out visit may include:

- Discussing timelines and strategies for the completion of outstanding forms
- Collect outstanding patient data forms and study forms such as the screening and monitoring logs
- Perform a final review of the study file documents
- Discuss the plans for record retention
- Discuss ongoing investigator responsibilities

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c.5. Statistical Analysis Plan

c.5.1. Data Management. The Data Management Group, part of the Coordinating Center, has primary responsibility for randomization, quality control, and analyses of data generated by the clinical centers. Data will be collected on hard-copy forms at each site and transferred to an electronic database. Our web-based management system will assure integrity and validity. Dynamic reports and periodic statistical analyses will monitor quality. A participant-based inventory system will track recruitment, retention, adherence, and missing data from entry through exit, close-out, and lock-down of final datasets. Our team developed a similar database for the IDEA and START studies (see Appendix F).

c.5.2 Statistical Analyses will be conducted and analyzed using to intention-to-treat principles in full accordance with the CONSORT guidelines (60). We will monitor SAEs on a regular basis to maintain up-to-date safety information for reporting to the DSMB.

c.5.3. Primary Aim. The primary hypothesis of long-term reduced WOMAC pain at 18 months will be tested based on a two-tailed significance level of 0.05 using contrast statements from a repeated measures mixed linear model with time (6, 18 mos), randomization arm (D+E vs control), and the interaction, which adjusts the means at each time point for potential missing data bias (61). Intervention-effect estimates will be further adjusted for baseline pain values, BMI, county, and gender; analysis will match design, so the variance estimate will not be biased. An unstructured covariance matrix will be used to account for the correlation between repeated outcomes at 6 and 18 months. In the unlikely event the model does not converge, a first-order autoregressive (AR[1]) covariance structure will be fit instead. Maximum-likelihood techniques will estimate parameters, as in the IDEA trial (14). Preliminary analyses will be conducted to check the shape of the distributions and variances between groups and as a function of the covariates of the prespecified models. Regression diagnostics and residual plots will help to find appropriate transformations, if necessary. We will include exploratory analyses of subgroups, defined by gender, age (<70 vs ≥70 years), baseline BMI (27.0-34.9, 35-44.9, ≥45 kg/m^2), clinic site, and race to determine any differential pain responses.

c.5.4. Secondary Aim 2. Repeated measures mixed linear models similar to Aim 1 will be used to analyze WOMAC function, 6-minute walk, and SF-36 physical subscale. Each outcome will be modeled separately, and 18-month effectiveness will be tested based on a two-tailed significance level of 0.05. The model will include the fixed effects study arm, time, time-group interaction, county, gender, baseline BMI, and baseline values of the outcome, and an unstructured covariance will be used assuming model convergence is not a problem (AR[1] otherwise). Analyses will be conducted to check the shape of the distributions and variances between groups and as a function of the covariates. Regression diagnostics and residual plots will help to find appropriate transformations, if necessary.

c.5.5. Missing Data. If missing data are related to outcomes, our results could be biased. We plan to account for missing data and conduct sensitivity analyses in accordance with the recommendations of the National Research Council (62). Our models will include variables from previous visits determined to predict loss to satisfy Little and Rubin's (63) conditions for data considered missing at random (MAR). If "informative censoring" occurs, we will compare analyses using subjects with complete data, multiple imputations, or explicit modeling of the censoring mechanism (64, 65).

Table 7: Power estimates for WOMAC pain, assuming baseline N=820, correlation between BL and 18 months=0.4, and common group SD = 3.50.

18 month Control Mean WOMAC Pain	18 Month D+E WOMAC Pain (% difference from Control)	18-Month Retention			
		70%	75%	80%	85%
		Power			
5.92	5.15 (13%)	81%	84%	86%	88%
	5.03 (15%)	91%	92%	94%	95%
	4.91 (17%)	96%	97%	97%	98%

c.5.6. Sample Size and Power Calculations

c.5.6.a. Primary Outcome *Aim 1*. Based on ADAPT, we expect the control group to reduce pain by approximately 10%; therefore, a 15% between group difference would require a 25% within group improvement from baseline, exceeding a minimally clinically important improvement (MCII) of 20% (2) (66). A total sample of 820 (410/group) will provide 94% statistical power to detect differences ≥15% in pain at the 2-sided 0.05 significance level with 80% retention (2-sample t-test, Nquery Advisor). In IDEA, the D+E arm reduced pain by an average of 51%, which

suggests the current assumptions are conservative. A total sample of 820 (410/group) will provide 94% statistical power to detect differences ≥15% in pain at the 2-sided 0.05 significance level with 80% retention at 18 months (2-sample t-test, Nquery Advisor). This approach utilizes the conditional variance approach of Borm et al. (67) for the estimation of power for ANCOVA models using group standard deviation $\sigma = 3.50$, Pearson correlation between baseline and 18-month pain score of $\rho = 0.4$ for a conditional standard deviation $\sigma_c = 3.21$ ($\sigma_c = \sqrt{1\text{-}\rho^2} \times \sigma$), and 18-month treatment WOMAC pain means ~D+E = 5.03 vs E-only control = 5.92 (Δ = -0.887). Variations of anticipated power due to modifications in retention and treatment effect are presented in Table 7. Correlation between baseline and 18 month pain values are estimated from the IDEA trial, while anticipated treatment effects and standard deviation for pain were obtained using weighted averages of D+E and non-D+E treatments from the ADAPT and IDEA studies, with some attenuation of the anticipated treatment effect due to the pragmatic nature of WE-CAN (Table 7).

c.5.6.b. Secondary Outcomes. *Aim 2*. Our sample size provides the ability to detect a moderate effect size of 0.234 at 85% power with relevant detectable differences. However, all estimates from IDEA and ADAPT were collected under rigorously controlled conditions; therefore the estimates for the pragmatic trial are conservative with respect to anticipated effect sizes. We assume in Table 8 a total baseline sample size of N=820, 80% retention at 18 months, and a 0.05 level of significance for all tests. The detectable and % differences from control aim to achieve 85% power. The mean differences in WOMAC function for D+E compared to D only and E only in IDEA were -3.3 and -4.3, respectively. Likewise, the differences in 6-minute walk distance for the D+E group versus D only in IDEA and ADAPT (41.5 and 42.1, respectively) indicate that the mean difference to achieve 85% power (15.2 m) is modest. IDEA indicated that SF-36 physical subscale was significantly improved in the D+E arm, with a difference of 2.8 (Table 8).

Table 8: Detectable absolute and relative (%) differences for secondary outcomes, n = 410/group, 80% retention, 85% statistical power, α = 0.05. Correlation between baseline and 18M values is *ρ*.

Variable	Anticipated 18m Control mean	Standard Deviation	ρ	D+E Mean (% change from Control)
WOMAC Function	17.5	11.5	0.6	15.3 (-12.3%)
Mobility: 6-Minute Walk (m)	509	90.7	0.7	524 (3.0%)
SF-36 Physical Score (0-100)	42.0	10.1	0.5	44.1 (4.9%)

18. Appendicies

A. Comparison of IDEA and WE-CAN

B. Intervention Sites

C. Organizational Structure, Committees, Committee Meeting Schedules

D. Diet-induced Weight Loss Group Session Topics

E. Attention Control Group Topics

F. Data Management and Quality Control

G. Manual of Operations

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