Weight Loss and Exercise To Improve Rheumatoid Arthritis Cardiovascular Risk

SWET vs CHAT Study

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Purpose of the Study

Aim 1: To determine if, compared to a counseling health as treatment (CHAT) program consistent with current standard of care, a 16-week supervised weight loss and exercise training (SWET) program improves cardiovascular risk in older, obese persons with RA.

Hypothesis 1a: Compared to CHAT, SWET produces superior improvements in metabolic syndrome (MSSc).

Hypothesis 1b: Compared to CHAT, SWET produces superior improvements in systemic inflammation, RA disease activity and monocyte/macrophage function.

Twenty-six older (ages 60-80 yr.), obese (BMI 28-40 kg/m2) persons with RA (seropositive or erosive) will be randomized to 16 weeks of CHAT or SWET. CHAT is a control arm based on traditional clinical counselling. SWET includes aerobic (3x/w) and resistance (2x/w) training plus a weekly weight loss session. At baseline and post-intervention, comprehensive assessments of "traditional" CV risk will include anthropometrics, blood pressure, body composition, cardiopulmonary exercise tests, and fasting blood for glucose, insulin and lipoprotein profiles. "Inflammatory" CV risk measures will include systemic inflammatory markers, disease activity (DAS-28) and monocyte/macrophage function.

The primary outcome variable is change in a highly validated, continuous z-score for metabolic syndrome (MSSc); MSSc are derived using participants' blood pressure, waist circumference, HDL-cholesterol, triglycerides, and glucose normalized to recommended threshold normative values. With 20 (accounting for 25% attrition) persons total completing both arms, we have 80% power (one-sided) to detect a difference in MSSc change of 1.8 ± 2.1, where each unit difference in MSSc corresponds to a HR for CV disease of 1.49 (CI 1.37, 1.62).

Aim 2: To determine if, compared to a CHAT program consistent with current standard of care, a 16-week SWET program improves patient-reported outcomes in older, obese persons with RA.

Hypothesis 2: Compared to CHAT, SWET produces superior improvements in self-reported global health, pain, fatigue, and physical function.

Baseline and post-intervention, global health, pain, fatigue, and physical function will be assessed using highly validated measures from the Patient Reported Outcomes Measurement System (PROMIS).

At the conclusion of this study, we will understand whether supervised weight loss and exercise training can improve overall RA CV risk as well as patient-reported outcomes. This work will generate effect sizes and identify critical components necessary for the design of future studies of less or more intensive interventions to improve RA CV risk. By demonstrating that improving body composition and physical activity meliorate current RA health disparities, this work should have immediate and long-lasting impacts on RA clinical care.

Background & Significance

Despite recent, revolutionary improvements in pharmacologic management, rheumatoid arthritis (RA) remains associated with increased rates of cardiovascular disease and mortality. RA cardiovascular risk results from a combination of traditional risk factors and RA-related systemic inflammation. Consequently, to improve overall RA cardiovascular risk, efforts should target both traditional risk factors and inflammation. One hypothetical means of improving overall RA cardiovascular risk is through weight loss and physical activity. Together, weight loss and physical activity can improve traditional cardiometabolic health through fat mass loss and skeletal muscle quality and functional gains. Additionally, disease-related cardiovascular risk will improve as both fat mass loss and exercise reduce systemic inflammation. To explore this hypothesis, 26 older, obese persons with RA will be randomized to a control intervention based on traditional clinical counseling or to a supervised weight loss plus exercise training program (3 times per week). Weight loss will occur via a dietitian-led intervention targeting 7% weight loss over 16 weeks, with weekly weigh-ins and group support sessions. Exercise training will consist of three times per week of an interval-based aerobic program plus twice-weekly resistance training. Both weight loss and exercise training will be supervised, via a scheduled Zoom live session, to maximize safety and adherence. The primary cardiometabolic outcome is a highly validated metabolic syndrome z-score, calculated from blood pressure, waist circumference, HDL-cholesterol, triglycerides, and glucose. RA-related cardiovascular risk will be assessed with measures of systemic inflammation, RA disease activity, and macrophage function – key cells at the nexus of rheumatic and cardiovascular disease activity. Intervention impacts on self-reported outcomes will be assessed with validated measures from the Patient Reported Outcomes Measurement Information System (PROMIS). This exploratory clinical trial will show whether a supervised intervention with weight loss and exercise training improves objective assessments of RA cardiovascular risk, disease activity and results in patients reporting overall improved health. This investigation will establish feasibility, acceptance, compliance, fidelity, and generate effects sizes critical for designing larger RA interventions, especially those comparing weight loss and physical activity amounts and types. Also, by demonstrating that weight loss with physical activity not only improves RA-associated cardiovascular risk and disease activity, but also patient-reported global health, this work should provide immediate and long-lasting impacts on RA clinical care.

Design & Procedures

Study design: Up to 30 adults, may be recruited and enrolled to participate in a cross-sectional study in order to account for screen failures and dropouts during the intervention period. We will stop enrollment after 26 persons have been consented and randomized; the target of 26 persons is to account for attrition after randomization. Occasionally, persons complete the consent process, yet decide not to participate prior to the initial assessments or randomization. We do not consider these persons in our post-randomization attrition calculations.

Our goal is for 20 subjects to complete the study. Subjects 60-80 yrs. of age will be randomized to one of two arms: 1) 16 weeks of a Counseling Health As Treatment (CHAT) program as a control arm designed to reflect traditional clinical counseling or 2) 16 weeks of a Supervised Weight loss and Exercise Training

(SWET) program including supervised aerobic and resistance exercise training plus a weekly weight loss session.

Phone Pre-Screening: Demographics and comorbidities will be assessed via self-report during an initial phone screening interview, with confirmation from the computerized medical record. Once it has been determined that the subject meets pre-screening criteria, they will be scheduled for Visit-1.

Study Schedule

Visit 1 - Consent will last approximately 1.0 hour.

On-site Consent: The consent process will take place in designated research space within the Aesthetics or Stedman buildings located at the Duke Center for Living campus.

Remote Consent: The study informational session is done one-on-one via a scheduled ZOOM meeting appointment with study staff. A secured REDCap platform will be used to obtain the participants' electronic consent (eConsent).

Brief Medical History, including list of medications, and PROMIS questionnaires: After obtaining consent, study staff will provide a link to a REDCap form to capture participant's demographics, medical history and a current medication list. In addition, participants will be asked to fill out some online questionnaires about their overall health, pain, fatigue, physical function, sleep and ability to manage their disease (PROMIS questionnaires). Completion of these measures will likely take between 10 and 12 minutes. Except for global health, scoring is performed by the computerized REDCap interface.

Visit 2 - Baseline visit will take place at the Duke Center for Living and will last approximately 2.5 hours.
Brief Medical History, including list of medications, and PROMIS questionnaires (If unable to complete prior to Visit 2)
Vitals: Resting Blood Pressure and Heart Rate
Anthropometric Measurements: Height/Weight/Body Mass Index (BMI) calculation
Blood Draw (Fasting)
Physical Examination
Physician RA Joint Assessment: Disease Activity (DAS-28) Assessment
NIRS Muscle Oxidative Capacity Test
Myoton Skeletal Muscle Biomechanical Measurement
Distribute 3-day Food Record

Anthropometric Measurements and Vitals: Anthropometric measurements (Height and Weight) will be obtained and BMI will be calculated. After the subject has relaxed in a seated position for approximately five minutes, resting blood pressure and heart rate will be measured.

Blood Draw: A study nurse will draw up to 150 mL of blood for complete blood count (CBC) with differential and platelet count, erythrocyte sedimentation rate (ESR), high-sensitivity C-reactive protein (hs-CRP), and immune cell function measures. CBC with differential and platelet count is a common

hematology test that is a measure of the number of different cells such as red blood cells, white blood cells, and platelets in the blood. ESR is another common hematology test that is a measure of inflammation. Except for those immune cell function assessments requiring immediate isolation of peripheral blood mononuclear cells, processed blood (plasma) samples will be stored in a -80ºF freezer for future assessments of immune cells, inflammation, and cardiovascular risk measures including components of the primary outcome, the metabolic syndrome score. Temporary storage is on the Center for Living Campus with transfer for long-term storage at the Duke Molecular Physiology Institute.

Physician RA Joint Assessment: Disease Activity (DAS-28) Assessment: Participants will receive a 28-joint examination by the study physician to assess RA disease activity and report their overall health assessment. In addition, participants will receive a brief physical examination.

Skeletal Muscle Mitochondrial Respiratory Capacity: Near-Infrared Spectroscopy (NIRS) will be used to measure oxidative capacity of forearm flexor digitorum profundus and medial gastrocnemius muscles using the PortaMon device (Artinis Medical Systems, The Netherlands). NIRS is a low-cost, non-invasive method that estimates muscle oxidative capacity by measuring oxygen consumption (mVO2) recovery kinetics via assessment of intramuscular oxy- and deoxy-hemoglobin concentration following a sequence of brief, rapid arterial cuff occlusions. NIRS measures mitochondrial oxidative function as the mVO2 recovery rate constant k. In the absence of blood flow, changes in muscle oxygenation occur via oxygen consumption alone. In persons without RA, this non-invasive approach is highly correlated with muscle respiratory capacity assessed via muscle biopsies using in situ permiabilized fiber bundles and the Oroboros O2k system.

Muscle Health and Function Test: Muscle health (tone, stiffness, and elasticity) will be assessed using the MyotonPro® device. Participants will lie supine on an examination table and will be asked to relax as much as possible. The research staff will create marks on the participant's skin for target locations of measurements on both sides of the body – the upper and lower arms, and the upper and lower legs. The MyotonPro® device (a small probe) will be placed on top of the skin overlying the muscle target followed by a brief and light impulse, which can barely be felt. This process will be repeated three times at each location. This test will take approximately five minutes.

3-day Food Record: Participant's current eating habits will be assessed using a 3-day food log.

Visit 3 - Baseline will take place at the Duke Center of Living and will last approximately 3.0 hours.

BodPod Body Composition and Waist Circumference Measurements
Leg Strength and Power Testing
Pulmonary Function Test
Cardiopulmonary Exercise Test
Collect 3-day Food Record
Pre- and post- CPET blood draw (optional)
Body Composition: Body composition assessments include waist circumference measurements and the BOD POD®. Minimal waist circumference measurements will be taken using a tape measure. This part will take approximately ten minutes. Following the circumference measurements, percent body fat

may be determined via the BOD POD® method. The BOD POD® test uses patented Air Displacement Plethysmography for determining percent fat and fat-free mass (muscle and bone). The test consists of measuring body weight using a very accurate electronic scale, and volume, which is determined by sitting inside the BOD POD® chamber. From these two measurements, percent body fat is calculated electronically. Spandex clothing and a swim cap are required and will be provided by the study staff. This test will take approximately twenty minutes.

Strength Testing: Strength assessments will include dynamometry-assessed grip and quadriceps strength (Cybex HUMAC NORM, Comp Sports Med, Inc., Stoughton, MA) tests.

Pulmonary Function Test (PFT): Pulmonary function will be assessed via spirometry, a non-invasive measure of lung function. Subjects will be asked to perform a series of breathing tests using a hand-held device. Subjects will be asked to breathe in and out as deeply or as quickly as they can for several seconds. The tests are repeated several times to ensure accuracy.

Cardiopulmonary Exercise Testing (CPET): Cardiorespiratory aerobic capacity (VO2 peak), will be assessed using a maximal treadmill test protocol with cardiopulmonary gas exchange. Subjects will be asked to exercise on a treadmill to their perceived maximum ability and effort during which time they will have a mouthpiece in their mouth to determine maximal oxygen use/consumption through breathing. For safety purposes the subject will be monitored by electrocardiogram (ECG) and their blood pressure will be measured at rest and throughout the exercise phase of this test. On-site medical supervision is provided during testing should an emergency arise. We have extensive experience with these assessments in various clinical populations.

Pre- and post- CPET blood draw: As part of a sub-analysis, participants will have the option to donate additional blood during this visit. If the participant agrees, a study nurse will obtain a baseline blood sample (~34 mL) prior to the exercise portion of the CPET. Participants will perform progressive aerobic exercise on the treadmill via CPET (explained above). Subsequent blood samples (~34 mL) will be obtained immediately (within ~5 minutes) and 30 minutes post-exercise. A total of up to 100 mL of blood will be collected via these 3 blood samples. Plasma and peripheral blood mononuclear cells/PBMC will be immediately isolated following blood draws and stored at -80°C. Plasma samples will be used for assessments of muscle-derived extracellular vesicles/EV (including proteomics and metabolomics) and peripheral cytokines (including IL-10, TGFb, INF-g, IL-17, IL-23, TNFα, IL-1b, IL-6, IL-15). PBMC samples will be used for assessment of CD4+ T cells (including flow cytometry subpopulation quantitation, proteomics, metabolomics, high resolution respirometry, and intracellular cytokines). Participation in this optional blood collection will allow scientists to learn more about the mechanisms of exercise effect on RA inflammation and immune function.

Visit 4 - Familiarization will take place at the Duke Center for Living and will last approximately 1.5 hours.

Randomization assignment
Distribute Activity Monitor, Exercise Resistance Bands, Weight Scale, and Tablet
Familiarization - distribute nutrition and exercise educational materials (participant take-home binder)

Randomization assignment: Participants will meet with a study staff for a familiarization session on how to use the devices. Regardless of the treatment arm, all participants will meet with both an exercise interventionist and a dietitian for further guidance.

Activity Monitors: A commercial activity monitor will be provided to all participants. Study staff will have online access to activity data to retrieve participant activity data and monitor intervention compliance. Our group has expertise in preparation of these devices for a variety of mobile interfaces, addressing regulatory issues pertaining to protecting web-based personal health information, and data management.

Exercise Resistance Bands: A set of exercise resistance bands will be provided to all participants. Each set contains 5 bands with varying levels of difficulty. Participants will receive guidance during Visit 4 on proper technique and utilization of the bands.

A&D Medical PLUSCONNECT Wireless Weight Scale: A wireless, Bluetooth enabled, digital scale will be provided to all participants to measure body mass. Study staff will be able to monitor the body weight of each participant throughout the course of the study via the Pattern Health app.

K10 Tablet: Participants will receive a tablet as a tool to help with exercise and nutrition compliance. The tablet will allow participants to download the required applications onto this device.

Familiarization: Participants will receive a binder containing nutrition- and exercise-related materials respective to the intervention arm. See 'Study intervention Methods' for more details.

Intervention: 16-week Ramp and Intervention Period [Study Intervention Methods are listed under Study Intervention section below]

Visit 5 - Post-Intervention visit will take place at the Duke Center for Living and will last approximately 2.5 hours.

Same Assessments as Visit 2

Visit 6 – Post-Intervention will take place at the Duke Center for Living and will last approximately 3.0 hours.
Same Assessments as Visit 3
Collect exercise journal from CHAT group only
Complete exit survey (online or in-person)

Exit survey: Participants will be asked to complete an exit survey regarding their experience with the program. Participants who withdraw from the study early will be asked to complete an exit interview with a member of our study team. The information collected will assist us with the development of future study designs.

End of study – After 26 participants have been enrolled, consented and randomized, the study will end when the last participant remaining in the study, completes the second post-intervention assessment visit.

Future follow-up studies – In the event of future follow up studies, participants will have the opportunity to volunteer as long as the current study protocol remains open. No contact information will be stored after closing this study protocol. By agreeing to this, participants will be contacted by a study staff once funding become available for future follow-up studies.

Failed assessments – In the event that a study assessment yields unreliable data due to an unanticipated issue, we would like to offer participants the opportunity to return for a repeat assessment. Participants will be asked to sign a consent addendum to complete a second attempt at a failed procedure. The designation of a failed procedure will be made according to the data quality guidelines outlined in the study assessment SOPs.

NOTE: Amd011 (APR.2023) - The study team would like the option to use testimonials from study participants enrolled in this trial in certain presentations (e.g. Medicine Grand Rounds). The study is closed to enrollment, so this would not be a recruitment tactic, this is simply a desire to share the positive health and quality of life benefits many of the participants in this clinical trial experienced as a result of the study intervention. Any subject testimonials that may reveal an individual's identity (i.e. a videotaped interview), would first require that the study team obtain a signed medical release from the participant.

Selection of Subjects

Participants with be recruited from the outpatient rheumatology clinics serving Duke Medicine and the Durham VA Medical Center. For our RA studies our most successful recruitment strategy is screening our clinical rheumatologists' charts; this method will be used unless recruitment goals are not met. First, we obtain permission from our clinical rheumatologists and then screen electronic charts of patients with recent visits for potentially eligible participants. With provider permission, we send potentially eligible participants letters from their provider introducing the study. These letters provide numbers for them to call for more information as well as to opt-out from a follow-up phone call from us. As an alternative strategy, if needed, we will perform a more global electronic search of medical records for persons with billing codes that identify rheumatoid arthritis RA, and recruitment letters/emails will be distributed. Additional recruiting, will occur through paper and electronic advertisements, doctor referrals, our Duke Health and Exercise Research registry and word of mouth. When interested persons call or are called, a standardized, IRB-approved phone screening process will be used to identify individuals eligible for the study. Age, height, weight, and a brief medical history will be asked only to determine whether study inclusion criteria have been met. Those interested in the study will be scheduled to attend a virtual or in-person consent session with study staff.

Population: The population is older obese persons with seropositive or erosive RA, not currently meeting US 2018 physical activity guidelines and without contra-indications to exercise or weight loss.

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

Inclusion Criteria
Ages 60 to 80 years.
Must have internet access.
Body mass index (BMI) 28-40 kg/m2.
Seropositive (positive rheumatoid factor or anti-citrullinated protein antibody) or erosions typical of RA on radiographs.

Exclusion Criteria
Subject unwilling/unable to utilize online platforms (e.g. ZOOM, REDCap, Pattern Health) for study activities.
Current use of biologic agents other than those targeting tumor necrosis factor alpha.
Current (within the last month) pharmacologic therapy with corticosteroids at doses greater than prednisone 5mg per day (or equivalent glucocorticoid doses).
Participating in regular exercise within the past 3 months (According to 2018 US guidelines: Not more than 150 minutes per week of moderate intensity exercise or 75 minutes per week of vigorous intensity exercise).
New medications within the last three months.
Medication dose fluctuation within the last 30 days.
Occurrence of coronary events consisting of occlusive disease (per cardiac catheterization or STEMI), acute heart failure, or documented dysrhythmia within the last 12 months.
Current presence of aortic stenosis rated moderate or worse
Diagnosis type 2 diabetes mellitus.
Other inflammatory arthropathy or myopathy, Paget's disease, pigmented villonodular synovitis, joint infection, ochronosis, neuropathic arthropathy, osteochondromatosis, acromegaly, hemochromatosis, or Wilson's disease.
Absolute contra-indications to exercise: Recent (<6 months) acute cardiac event, unstable angina, uncontrolled dysrhythmias causing symptoms or hemodynamic compromise, symptomatic aortic stenosis, uncontrolled symptomatic heart failure, acute pulmonary embolus, acute myocarditis or pericarditis, suspected or known dissecting aneurism or acute systemic infection.
Relative contra-indications to exercise: Left main coronary stenosis, moderate stenotic valvular heart disease, outflow tract obstruction, high degree AV block, ventricular aneurysm, uncontrolled metabolic disease (e.g. diabetes, thyrotoxicosis, myxedema), uncontrolled pulmonary disease (e.g. severe COPD or pulmonary fibrosis), mental or physical impairment leading to inability to exercise adequately.
Significant weight change (gain or loss of > 10 pounds in 1 month) within the past 6 months.
Unwillingness or inability to adhere to the diet structure of the study.

Subject Recruitment and Compensation

Patients with RA will be recruited from Duke Rheumatology Clinics, including “off-campus” locations South Durham and Brier Creek. Patients may be contacted in advance of their appointment by reviewing the screening schedule (see waiver of consent). Patients that may be contacted in advance of their

appointment, may be contacted via IRB approved letter, phone script, and/or email template. The recruitment email will be sent from a shared study email address, SWEAT@dm.duke.edu.
Patients that have opted out of research contact, via yellow dot in Maestro, will not be contacted. Patients will not be contacted more than three times, including via letter, phone, email, and face-to-face interaction. If a patient states they would like to opt out, the study team will follow the Duke Recruitment and Engagement policy.

Additional avenues for RA participant recruitment are as follows:
Self-referral through phone call or email via advertisement on Duke Health and Exercise Research Trials Website (https://dmpi.duke.edu/duke-health-and-exercise-research-trials) and flyers posted in Duke Rheumatology Clinics
Direct referral from rheumatology provider
Identification via electronic health record (EPIC) search using Slicer Dicer
The study will be advertised at the Duke Rheumatology Divisional Grand Rounds every 3 months
IRB approved Flyers advertising the study may be given to all Duke Rheumatology clinicians
Direct contact (phone call and/or email) of volunteers registered through the Duke Health and Exercise Research Trials Registry (https://dmpi.duke.edu/duke-health-and-exercise-research-trials-registry)

IRB approved Flyers/posters may be posted in public areas of Duke Hospital, Duke clinics, CFL bulletin boards (e.g. the fitness center), public venues (e.g. Duke Farmer's Market) and throughout the community with permission, websites (e.g. DMPI website), social media venues (e.g. DMPI Facebook page; Instagram), print ads, and/or internet ads. Potential subjects for this study may also be directed to contact the recruitment coordinator to obtain more information about the study, if interested. When contacted, the recruitment coordinator will confirm the participant meets most of the inclusion/exclusion criteria before scheduling him/her for a consent meeting. Phone screening will assess whether the individual meets the major criteria and, after explanation of the study purpose and protocol, if the individual is still interested, study staff will review their medical record for screening purposes. If eligible, they will be invited to attend an information session that will be conducted by the study coordinator or another member of key personnel to present the details of the study. We will allow up to 60 minutes for the subjects to read the consent, ask questions and decide whether or not they are willing to participate in the study.

Compensation: All study participants will receive about $300 worth of health-related equipment, a physical activity monitoring device, a set of resistance bands, a tablet for viewing physical activity data, and a Bluetooth enabled digital scale. These will be accompanied by instructions for use from our dietitians and exercise physiologists. Additionally, participants will be reimbursed a total of $200 for completing the entire study to cover expenses related to their participation. Participants will receive $50 upon completing both baseline visits and will receive $150 for completion of the intervention and both exit visits. If a subject leaves the study early, or if the PI must withdraw them from the study, they will be paid only for the visits they have completed.

Study Interventions

After informed consent and baseline assessments, participants will be randomized to the SWET intervention arm or the CHAT control arm.

A. SWET Arm: The SWET arm consists of three components: weight loss, aerobic training, and resistance training.

A.1. SWET Weight Loss Component

Initial Session and Prescription: Participants meet individually at baseline with a registered dietician to receive an individualized kcal prescription. Prescriptions are calculated as below using participant data and estimated total energy expenditure (TEE):

--TEE for Obese Men: 864 – (9.72 x Age [y]) + PA x (14.2 x Weight [kg] + 503 x Height [m].

--TEE for Obese Women: 387 – (7.31 x Age [y]) + PA x (10.9 x Weight [kg] + 660.7 x Height [m]).

The prescribed calorie level for a weight loss of ~1-2 pounds (average of 0.6 kg) per week will be based on a reduction of 500 to 1000 kcal/day below TEE; the 16-week target is 7% weight with an expected achievement of 5%. The macronutrient distribution of the SWET diet will be 40% carbohydrate, 30% fat, and 30% protein.

Ramp Period: The initial weeks of the curriculum focuses on utilization of dietary exchanges and understanding of the diet prescription with progression towards more complex topics.
Diet Fidelity: Diet compliance will be monitored by weekly weigh-ins and weekly collection of daily food journals. Weight and dietary intake will be captured via A&D scale and My Fitness Pal. Additionally, participants will utilize a weight loss graph to track their weight loss throughout the 16 weeks. At baseline, 8-, and 16-weeks, 3-day food diaries will be collected to determine diet intake (kcal, macronutrients and micronutrients) using Food Processor Version 11.0. 2015, ESHA Research.

Adherence: Study interventionists will be guided in a consistent and measurable approach using an algorithm to identify participants that are at risk of non-compliance and dropping out of the study. Based upon our previous utilization of the Ecological Model and Social Cognitive Theory and our own experience in clinical practice, we developed a “toolbox” of resources available to reduce participation barriers and address challenges to diet adherence likely to be encountered in obese older adults with RA (see Toolbox attached). When the algorithm is “triggered” by indicators of poor adherence, interventionists will begin to utilize intervention tools according to the flow described.

Site: All sessions take place remotely via a one-on-one Zoom appointment. If desired, appointments can also take place at the Duke Stedman Center for Nutrition which has rooms available for individual counselling, an auditorium used for group sessions, and plentiful free parking.

A.2. SWET Aerobic Exercise Training Component:

Frequency, Intensity, Duration: Aerobic exercise training will be remotely supervised using a platform health program for staff to review daily exercise and using a once weekly virtual in-person class. For classes, participants will be performing exercises, at home or an alternative location with internet access. As part of initial in-person assessments, participants' fitness level will be determined by a cardiopulmonary exercise test with gas exchange. Using each individual's fitness level, individualized exercise prescriptions and instructions will be developed by study staff. Staff will instruct participants to reach a prescribed amount of active minutes and step count per week (recorded by their Garmin watch). Each participant's exercise prescription will include required attendance at a "virtual in-person" live online aerobics class. This weekly class will be led by a study staff member; in addition to serving as remote supervision, this class will promote exercise compliance and reduce attrition. This supervised training will be approximately 60 minutes long, consisting of a warm up and cool down period and moderate aerobic moves that can be done without the need of any exercise equipment. Each class will end with a stretching session. During these exercise training sessions, participants will monitor heart rates with wrist worn devices and with staff assistance, modify as needed aerobic moves to maintain heart rates within the prescribed range. The prescribed range will equate to 45-65% of VO2 reserve. A pre-recording of the exercise moves will be available on our study YouTube page for participants to view at any given time.

In addition to the remotely, supervised live virtual exercise class, participants will be instructed to perform aerobic exercises on their own in order to meet both their step-count and active-minutes goal. Aerobic exercises they can perform remotely are: walking, running, dancing, and aerobics workout videos. On average, participants will aim to accumulate 150 minutes of aerobic physical activity and a minimum of 6,000 steps per week. Participants will upload step counts and active minutes daily, typically each evening as part of device battery charging. Staff will review data at least once a week to ensure data are being uploaded. As needed, weekly calls from staff to participants will be used to discuss problems with devices (i.e., data uploading) or exercise (i.e., general barriers, difficulty maintain heart rates in the target range).

Prescription: Prior to initiation of training, each participant will undergo a cardiopulmonary exercise test for determination of VO2 reserve. Prescribed intensity ranges (i.e. 45-65% VO2 reserve) correspond to heart rate reserve (HRR), calculated as maximum – resting heart rate. Target HRR ranges are monitored by heart rate monitors worn during training sessions, which will then be available for study staff members to see via the Pattern Health application and through the Garmin website. During the virtual classes or weekly calls, participants will be counseled if target HRR ranges are too low or too high based on their personalized prescription.

Ramp Period: During this ramp period, study staff will counsel participants on understanding device use, heart rate ranges, and exercise safety. Study staff will also discuss exercising at initial intensities and heart rate ranges corresponding to lower intensities. During this ramp period, study staff will offer guidance virtually or in-person with exercise training as well as provide assistance with issues regarding study equipment. Over time, intensities will progressively increase along with a corresponding target heart rate range.

Mode: Exercise videos will be available on our study YouTube page for participants to view at any given time. Besides the live virtual exercise class, participants will be held accountable to perform aerobic exercises on their own in order to meet both their step-count and active-minutes goal. Aerobic exercises they can perform remotely are: walking, running, dancing, and aerobics workout videos.
Aerobic Training Fidelity: During the supervised virtual exercise class, participants will be instructed by study staff to maintain a target heart range. If the participant has difficulty maintaining or reaching the target heart rate range, a virtual one-on-one training session with the exercise physiologist will be scheduled and the training intensity will be modified accordingly. For activity outside of training sessions, participants use the study-provided commercial activity monitors which show "real-time" heart rates and daily accumulated step counts. Activity monitor data will be downloaded for computerized analysis.

A.3. SWET Resistance Exercise Training Component:

Frequency: Participants will be prescribed twice weekly resistance training sessions, with each resistance session separated by ≥48 hours.
Exercises, Sets, Repetitions, and Intensity: For each of the 10-11 exercises that target major muscle groups, a ramp period over four weeks of 1-3 sets of 8-15 repetitions will be performed at an initial intensity determined by the exercise physiologist during the initial familiarization session with the participant. Participants will be instructed to perform resistance superset exercises with a rest period of 60 seconds between each set.

Prescription: A familiarization session with an exercise physiologist will introduce participants to the exercise bands, targeted muscle groups, and proper technique. After a warm-up period, the exercise physiologist and the participant will work together to decide on a comfortable resistance band to use for each of the 10-11 exercises to determine an individualized exercise prescription. The starting band will be set when the participant can perform 6-8 repetitions comfortably using proper technique with a Rating of Perceived Exertion (RPE) between 12-14.

Progression: Over 16 weeks, the amount of resistance lifted and/or repetitions will be slowly increased such that progression occurs while minimizing musculoskeletal injuries. After two back-to-back training sessions during which 1-3 sets of 15 repetitions were performed with proper technique, the resistance will be increased (typically 5-10%) such that 1-3 sets of 8-10, but not 15, repetitions can be properly performed.

Training Fidelity: Safe and effective exercise technique will be emphasized to promote full range of motion, activation of targeted muscle groups, and proper breathing to prevent the onset of the Valsalva. Training staff and participants will record exercise training data using the Pattern Health app or on log sheets for additional verification.

Site: All initial cardiopulmonary exercise tests and strength testing as well as initial familiarization sessions will be performed at the Duke Center for Living, supervised by an exercise physiologist. Subsequently, exercise will be performed typically in the participants' home or neighborhood, with only restrictions being adequate internet access for the virtual training sessions and an environment allowing

safe exercise in the prescribed heart rate ranges. Weekly calls will include discussions of these environments, especially if barriers to safety or prescribed ranges arise.

B. CHAT Arm: Participants randomized to the CHAT arm receive counseling on healthy diets and physical activity. Sessions below occur after baseline assessments and randomization.

B.1. Diet Counseling: Participants meet one-on-one for 20- to 30-minutes with a Registered Dietitian (RD) for dietary recommendations to improve overall health. Recommendations will be to (1) Follow healthy eating patterns; (2) Focus on variety, nutrient density, and amount; (3) Limit calories from added sugars and saturated fats and reduce sodium intake; (4) Shift to healthier food and beverage choices; and (5) Support healthy eating patterns. Summaries of these recommendations will be provided.

B.2. Diet Fidelity: Participants will monitor diets with a food journal. At baseline, 8 weeks, 16 weeks and 24 weeks, 3-day food diaries will be collected to determine diet intake (kcal, macronutrients and micronutrients) using Food Processor Version 11.0. 2015, ESHA Research.

B.3. Physical Activity Counseling: Participants meet one-on-one with an exercise physiologist for recommendations for physical activity to improve overall health. Aerobic activity recommendations will be to target at least 6,000 steps per day and five 30- to 35-minute walking sessions per week. Discussions include first, how to assess daily steps and second, to increase daily steps each week until the 6,000 step per day target is reached. Walking will be recommended at a moderate intensity and described as “able to carry on a brief conversation but not able to sing” or as a 12-14 on a 20-point scale of exertion. Resistance training recommendations will be two sessions per week, each separated by 48 hours. Instructions for 8-10 upper and lower body resistance exercises using Thera-bands will be reviewed; Thera-bands and written summaries will be provided.

B.4. Physical Activity Fidelity: Participants be provided with commercial activity monitors and an exercise journal to record daily steps, walking sessions, and resistance sessions. Each week for 16 weeks, activity monitor data will be downloaded for computerized analysis.

B.5. Minimize Attention Bias: Study staff will connect with CHAT participants once a month to ensure they don't have any questions or concerns.

Risk/Benefit Assessment

RISKS:
Blood Draws: There is a risk of local pain, soreness, bleeding, bruising and swelling, as well as light-headedness, dizziness and rarely, fainting and/or a local infection.
Bod Pod: This test may not be comfortable for anyone who has felt claustrophobic (uncomfortable in small places) before but is generally well tolerated.
Pulmonary Function Test: This is a non-invasive procedure. Dizziness during the breathing maneuvers, feeling short of breath, coughing, asthma attack brought on by deep inhalation are possible side effects.
Cardiopulmonary Exercise Test: The risks of the cardiopulmonary exercise test include but are not limited to: fainting, falling, irregular heartbeat, wheezing and shortness of breath, and very rarely, heart

attack or death (less than 1 in 10,000 cases). Participants will be given careful instruction prior to, and during, exercise testing to determine when it is appropriate for them to stop exercising. The exercise test will be performed under the supervision of medical staff who are equipped to deal with emergencies.
NIRS: This is a non-invasive procedure. Site deformation to the skin, redness or bruising may occur momentarily while the cuff is inflated during the assessment.
Exercise Training: Participation in an exercise program may result in muscle, bone and/or joint soreness, discomfort and/or injury.
Mobile Applications: Information collected by mobile applications or 'apps' is subject to their terms of use, which participants should read carefully. Many apps make claims that they are very secure, compliant with federal privacy regulations, and used and tested by other academic centers. However, any mobile app that is downloaded carries potential security risks, and Duke cannot guarantee that these mobile apps are free of risk. Some apps may be able to perform hidden functions or may have security flaws that allow unauthorized access to information. We are unable to fully tell subjects what information these mobile apps are able to access or change on their device (phone/tablet) or what information from their device may be stored outside of Duke. Subjects will be encouraged to limit personal identifiers they enter into mobile applications (particularly their name, date of birth, address, place of employment, and other details that could allow someone to identify them) only to those that they wish to voluntarily share with others. These apps may send/receive information with other mobile apps, including social networking apps or websites (for example, Facebook). If the subject gives permission for this, the terms of use for those apps/websites apply and they should read them carefully.

It is recommended that the subject run a current operating system (OS) on their device, review the privacy/security settings often, and restrict any unnecessary access. These applications may run in the background of their device. Mobile apps may have an unanticipated impact on the operations of their device (e.g., battery drainage). If they do not have an unlimited data/text plan, they may incur additional charges. At the conclusion of the study, we will provide the subject instructions on how to remove the mobile apps from their device or assist them with the process if requested.

We are not asking the subject to make any health decisions based on the use of these mobile apps. The subject will be told to discuss health decisions directly with their healthcare provider.

As with all technology, the subject will be asked to wait until they are in a safe environment, use good judgment and follow prevailing laws. Do not perform study-related activities while they are driving.

In addition to the risks listed above, the subject may experience a previously unknown risk or side effect.

POSSIBLE BENEFITS: We cannot and do not guarantee that a subject will receive any benefit from taking part in this study. Their willingness to take part may, however, increase knowledge regarding the treatment of RA and help future subjects. Several likely benefits include the following:

Subjects will have physical examinations and laboratory tests provided to them at no cost. The study doctor will share with a subject any findings on these tests that indicate a potential problem.
Participants randomized to SWET will receive exercise physiologist-supervised exercise training and

ongoing, dietician-delivered feedback about diet and weight loss. Participants randomized to CHAT will receive one-on-one counselling about proper diet and exercise recommendations. Upon study completion, CHAT graduates will have the opportunity to join the weekly group nutrition classes in addition to gaining access to the study YouTube exercise channel link; therefore, CHAT graduates will receive the same educational materials as the SWET group upon finishing the study. These benefits are well-recognized as contributing to overall improved health.

WHAT IF THEY CHOOSE NOT TO PARTICIPATE IN THIS STUDY: If a subject does not want to take part in the study, they have the choice to undergo standard treatment for RA. If a subject decides not to take part in this study, their decision will have no effect on the quality of medical care they receive.

Data Analysis & Statistical Considerations

Primary Outcome: Assessing cardiovascular (CV) risk in RA is controversial. Despite general consensus that RA disease activity contributes to CV risk, RA-specific risk calculators perform similar to calculators designed for general populations. Additionally, most calculators use presence or absence of risk factors, which, especially for type 2 diabetes, coronary disease, or tobacco use are unlikely to be reversed in a 12 week non-pharmacologic intervention. Based on this, we elected to exclude those conditions and assess cardiometabolic risk with continuous metabolic syndrome z scores (MSSc). MSSc have accuracy similar to Framingham risk scores and will reflect expected improvements in cardiometabolic variables. MSSc are calculated using differences between Adult Treatment Panel III guideline values and participant values for mean arterial blood pressure, minimal waist circumference, fasting HDL-cholesterol, triglycerides, and glucose with normalization to the cohort standard deviations. We have experience calculating and showing intervention responses with MSSc.

Expected Effect Size and Power: Sample size calculations seen in Table 1 are based on data from our Co-Investigator, Dr. Kraus', work in STRRIDE (Studies of Targeted Risk Reduction Interventions through Defined Exercise), a series of randomized controlled studies of exercise training with and without weight loss in persons at-risk for cardiovascular disease, but without RA.

These data show that relative to a Control group with little change in MSSc, aerobic training and weight loss improve MSSc by -2.5 ± 2.1. Based on these we would expect similar improvements in our supervised intervention arm (SWET) that includes each of aerobic training, weight loss, and resistance training. Yet, because the SWET 16 week intervention period is on the shorter end of the 16-24 week STRRIDE interventions, full improvements may not be completely achieved. To detect a significant difference between SWET and, the counseling control arm (CHAT) of 1.8, assuming a standard deviation for change of 2.1, 20 persons total will deliver 80% power with a one-tailed alpha of 0.05. We justify a one-tailed test based on our hypothesis that the SWET will significantly exceed CHAT for metabolic syndrome score reduction and that CHAT exceeding SWET, is implausible. Based on our prior experience, we expect an attrition rate of 25% during the intervention period, randomizing a total of 26 RA participants to achieve 20 participants completing the intervention.

Statistical Methods: To assess the difference between SWET and CHAT with respect to the primary and secondary outcomes, we will create change scores (Post-intervention – Pre-intervention) and use linear

models to assess group differences. Distributions will be assessed, and nonparametric methods used or transformations performed if the distribution of the outcomes are non-normal. We will control for important baseline variables, including baseline levels of the outcome of interest. Non-adherent individuals, including those failing to complete the intervention, will be analyzed as specified under an intention-to-treat criterion. Statistical significance will be established as $P<0.05$ (one-tailed) for the primary outcome, MSSc.

Secondary and exploratory outcomes will be tested at $P<0.05$ without Type-I error control for multiple outcomes. When results are reported, we will alert the reader of the P-value issues inherent in the testing multiple of multiple outcomes. This rich database can be used for exploratory analyses, including mediation, moderation, and mechanism; examples include (a) if level of compliance impacts level of change in the CV measures, (b) if change in one CV measure impacts change in other measures (possibly irrespective of group), and (c) interactions. The analyses will proceed chronologically in 4 phases.

Descriptive analyses that will summarize the distribution of the covariates and dependent variables. Bivariate analyses of the association between group membership and the outcome measures. Controlled multivariable analyses, which assess the association between intervention arm and the outcomes controlling for the important covariates – prespecified prior to analysis (see below). Controlled multivariable analyses, which assess the association between outcomes and potential mediators controlling for the important covariates.

Correlation of all outcome changes, which will assess if the intervention has a generalized change across all outcomes, or, is specific to varying outcomes depending on the person. This exploratory analyses may lead to models that predict what kind of person changes in this area but not some other area. While we recognize we have limited power for these exploratory analyses, they may lead to future investigations of individualized prescriptions for weight loss and exercise for certain outcomes. Inclusion of covariates, such as the baseline measure for the outcome of interest, into the models will add precision to the estimates and allow us to assess the generalizability of the effects across the covariates. The list of covariates (i.e. age, race, gender, BMI, disease activity) will be developed prior to any analysis.

Handling of “dropouts”: In addition to intention-to-treat analyses described above, rates of non-adherence and lack of completion will be assessed. The sample that completed versus those that did not will be compared with respect to demographic and clinical differences. These analyses will help improve adherence in future studies as well as to determine any potential impact of dropouts on the findings.

Handling of missing data from participants completing the intervention: Every effort will be made to ensure complete data on all participants. However, occasions arise (e.g. unable to obtain sufficient blood for monocyte functional analyses) where data will be unavailable. Missing data will be assessed for whether it is missing at random, missing completely at random, or missing not at random. For the first two, pair-wise deletion of missing data (If the post-intervention value is missing, the pre-intervention value will be deleted.) will be performed prior to analyses of group differences. If missing

not at random (Missing values are more common in the control arm, one sex, or other critical measure), multiple imputation methods will be used prior to analyses of group differences. Missing data and imputation methods will be reported.

As of 12/8/23, Dr. Kim Huffman at Duke has entered into a Materials Transfer Agreement (MTA) with Genos Glycoscience Research Laboratory (Genos) to send de-identified plasma samples associated with Pro00104843. The purpose for sending the samples to Genos is to measure IgG N-glycosylation and plasma N-glycosylation. All identifiers have been removed and Genos will not be provided with any information that could be used to identify the study participants. Results will be returned to Duke.

Data & Safety Monitoring

Adverse Event: An adverse event is any untoward medical occurrence in a participant randomized into this study and which does not necessarily have to have a causal relationship with their participation. An adverse event can therefore be any unfavorable and unintended sign (for example, an abnormal laboratory finding) or symptom temporally associated with their participation in this study.

Unanticipated Problem: Unanticipated Problems are not defined in 45 CFR Part 46, but are defined by the OHRP as any incident, experience or outcome that meets all of the following requirements:

1. Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
2. Related or possibly related to participation in the research. Possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
3. Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Serious Adverse Event: A serious adverse event is any untoward medical occurrence that results in death, is life-threatening, and requires inpatient hospitalization or results in prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a medically important event.

Protocol Deviation/Violation: An inadvertent act (from the perspective of the PI and study staff) in which the protocol is not followed. An example of a protocol deviation is, an accidental misread of a laboratory value as being within the reference range when it actually is sufficiently abnormal to preclude study participation by the subject. A protocol violation is an intentional act (from the perspective of the PI and study staff) in which the protocol is not followed.

The NIAMS reporting requirements for Adverse Events (AEs), Serious Adverse Events (SAEs), Unanticipated Problems (UPs) and Protocol Deviations, as indicated below:
All non-serious AEs will be reported in aggregate to the Internal SO and the NIAMS (through the NIAMS Executive Secretary) as part of the routine safety report.

All SAEs (regardless of related ness or expectedness) will be reported to the NIAMS (through the NIAMS Executive Secretary) and Internal SO within 48 hours of the PI becoming aware of the event.
All UPs determined by the PI to be a non-serious AE will be reported in aggregate to the Internal SO and the NIAMS (through the NIAMS Executive Secretary) as part of the routine safety report. Those UPS determined by the PI to be an SAE will be reported to the NIAMS (through the NIAMS Executive Secretary) and the Internal SO within 48 hours of the investigator becoming aware of the event.
Protocol deviations impacting participant safety will be reported to the NIAMS (through the NIAMS Executive Secretary) and Internal SO within 48 hours of the PI becoming aware of the event; all other deviations that do not impact participant safety will be reported as part of the routine biannual safety report.

All reportable AEs will be submitted per the following DUHS IRB policies below:
An Adverse Event must be reported to the IRB if it: (i) is more likely than not related to study activities; and (ii) represents a new risk; and (iii) is unanticipated. In addition, an expected event that is occurring at a frequency or intensity greater than originally anticipated must be reported within ten business days of the investigator becoming aware of the event, study personnel will send to the IRB a Safety Event submission in iRIS.
For a reportable Serious Adverse Event, study personnel will notify the IRB within five business days of the investigator becoming aware of the event. Study personnel will send a Safety Event submission in IRIS.
For any other Unanticipated Problem or event requiring prompt reporting to the IRB, within ten business days of the investigator becoming aware of the event, study personnel will send to the IRB a Safety Event submission in IRIS.
Immediately (within 24 hours) upon learning of an unanticipated study-related death, study personnel will notify the IRB via phone or email by providing a brief summary of the event. Then within 1 week (five business days), study personnel will send to the IRB a Safety Event submission in iRIS.
A Protocol Deviation/Violation must be reported to the IRB if it: (i) affects subject rights and welfare, or (ii) affects subject safety; or (iii) affects the integrity of study data; or (iv) affects the subject's willingness to continue in the study; or (v) is specifically requested by a government agency, internal/external auditor, medical monitor, or the IRB.
Time Period and Frequency of event assessment and follow-up: The clinical course of each adverse event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause.

How will Participants be informed: Study participants will be notified by the PI, or study team, should an AE, SAE or UP occur that impacts the following: i) affects subject rights and welfare, or (ii) affects subject safety; or (iii) affects the integrity of study data; or (iv) affects the subject's willingness to continue in the study; or (v) is specifically requested by a government agency, internal/external auditor, medical monitor, or the IRB.

Describe plans for detecting and managing incidental findings associated with study Procedures:
An incidental research finding is an abnormality discovered in the course of this research for which there is a potential health importance. During the Cardiopulmonary Exercise Test (CPX) assessment, the subject will be connected to an electrocardiogram (ECG) machine to monitor their heart rate and

rhythm. Once the CPX is complete, the ECG will be reviewed by a Cardiologist just as it would be if they were having the CPX as part of their routine medical care. There is a possibility that while reviewing the ECG, the Cardiologist may see an abnormality defined as a possible “Positive” stress test, or the presence of some other abnormal electrical conduction. This is what is called an "incidental finding." If an incidental finding occurs, the following Action Plan will be implemented:

Action Plan: We will contact the subject if the Cardiologist interprets the CPX test as “Positive”. Study staff will ask the subject for their permission to give information about this incidental finding to their primary doctor and we will offer to refer them to an appropriate doctor for further evaluation. Follow-up testing will be required in order to participate in this study. The costs for any care that will be needed to diagnose or treat an incidental finding would not be paid for by this research study. These costs would be the subject’s responsibility.

Clinical site monitoring will be performed utilizing an Institutional approved CQMP plan.

The trial will be conducted in compliance with the protocol, International Council for Harmonization/Good Clinical Practice requirements (ICH/GCP), and applicable state, local and federal regulatory requirements.