

**Targeting Physical Health in Schizophrenia:
Physical Activity Can Enhance life
(PACE-Life)**

Clinical Protocol

Version 1.0

Protocol Date: June 4, 2020

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ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
6MWT	6-minute walk test
ACSM	American College of Sports Medicine
AE	Adverse Event
BMI	Body Mass Index
BPNES	Basic Psychological Needs in Exercise Scale
BREQ-2	Behavioral Regulation in Exercise Questionnaire-2
CRF	Cardiorespiratory fitness
CVD	Cardiovascular Disease
DSC	Data Safety Committee
DSM-V SCID	Structured Clinical Interview for DSM disorders
FDA	Food and Drug Administration
HRR	Heart Rate Reserve
IPAQ	Short Form International Physical Activity Questionnaire
NCPRC	North Carolina Psychiatric Research Center
OPTMH	Organization of Physical Therapy in Mental Health
PA	Physical Activity
Pace-Life	Targeting Physical Health in Schizophrenia: Physical Activity Can Enhance life
PACES	Physical Activity Enjoyment Scale
PANSS	Positive and Negative Syndrome Scale PANSS
PAR-Q	Physical Activity Readiness Questionnaire
RCT	Randomized Control Trial
RHR	Resting Heart Rate
SAE	Serious Adverse Event
SDT	Self-determination Theory
SSD	Schizophrenia Spectrum Disorder
STEP	Schizophrenia Treatment and Evaluation Program
WASI	Wechsler Abbreviated Scale of Intelligence

PROTOCOL SYNOPSIS

Study Title	Targeting Physical Health in Schizophrenia: Physical Activity Can Enhance life (PACE-Life)
Funder	National Institutes of Health
Clinical Phase	Phase I
Study Rationale	The purpose of the PACE-Life trial is to develop and test the feasibility of an exercise intervention that combines group walking, activity tracking, and heart rate monitoring, and determine the effectiveness of this intervention on the physical and mental health for individuals with schizophrenia spectrum disorders.
Study Objective(s)	<ol style="list-style-type: none"> 1. Feasibility- Can PACE-life be delivered within this treatment setting? 2. Tolerability- How well is PACE-life accepted by the subjects? 3. Intervention adherence 4. Evaluation of PACE-life
Test Article(s) <i>(If Applicable)</i>	Fitbits Charge HR devices, worn on the wrist, will be utilized to track daily steps, minutes spent walking, and monitor HR throughout exercise sessions. These devices will also be used to facilitate the individualized/home-based component and goal-setting.
Study Design	This is a one arm, open trial with 14 subjects (two groups of 7 subjects conducted concurrently).
Subject Population key criteria for Inclusion and Exclusion:	<p><u>Inclusion Criteria</u></p> <ol style="list-style-type: none"> 1. DSM-V diagnosis of a SSD (Schizophrenia, Schizoaffective Disorder, Brief Psychotic Disorder, Schizophreniform Disorder, and Unspecified Schizophrenia Spectrum and Other Psychotic Disorder) 2. Between the ages of 18-65, both genders, and any ancestry; 3. IQ>70. IQ will be assessed using the Wechsler Abbreviated Scale of Intelligence (WASI) 4. No hospitalizations for psychiatric reasons in the last 3 months 5. Clinically stable (no psychiatric medication changes within the past month) 6. Are not already engaging in consistent moderate-intensity exercise (cutoff = 60 min/week for the past 6 months); 7. Present with no contra-indication to engage in regular moderate intensity exercise based on the American College of

Sports Medicine guidelines. (If an individual answers yes to one item on the of the Physical Activity Readiness Questionnaire (PAR-Q), she/he will be asked to get clearance from a physician prior to participating in the study)

8. Willing and able to provide informed consent.

Exclusion Criteria

1. Pregnant women will be excluded because pregnancy alters autonomic and immune responsiveness, increase weight gain, and can influence heart rate.

Number Of Subjects	14 individuals with schizophrenia spectrum disorders
Study Duration	Each subject’s participation will last 7 months, 6 months of intervention and a 1 month follow-up
Study Phases	<u>Pre- Screening-</u> Will be completed prior to the first in-person visit via a telephone screen for study eligibility.
Screening	
Study Treatment	<u>Screening-</u> Subjects who are deemed eligible will be brought on site to obtain consent and complete the screening assessments (Demographics, WASI, a licensed physician will complete a medical history and physical exam, PAR-Q.
Follow-Up	<u>Baseline, Mid-point, Post-test, and 1-Month Follow-up-</u> Subjects will complete the Demographics, Minutes Spent Walking, the Positive and Negative Syndrome Scale (PANSS), the Short Form International Physical Activity Questionnaire (IPAQ), Steps/day, Cardiorespiratory fitness (CRF)- CRF will be measured using the 6-minute walk test (6MWT), Self-determination Basic Needs, the Basic Psychological Need Scale-in General, the Basic Psychological Needs in Exercise Scale (BPNES), Resting Systolic/Diastolic Blood Pressure and resting heart rate (RHR), autonomous motivation will be measured with the Behavioral Regulation in Exercise Questionnaire-2 (BREQ-2), enjoyment of walking will be measured with the Physical Activity Enjoyment Scale (PACES), the UCLA Loneliness Scale, Weight, BMI, and Waist/hip Circumference: study intervention/experimental treatment. At the baseline assessment, subjects will be provided with a Fitbit wristband and instructed how to use it. At the conclusion of the trial, investigators will administer a brief questionnaire to the subjects regarding satisfaction and acceptability.
	<u>Study Treatment-</u> Walking groups will occur twice per week for 30 minutes. The intensity of both group walks and home-based walks will increase throughout this intervention in a stepwise fashion to create an exercise dose response to maximize impact on CRF.

Efficacy Evaluations	<p><u>Primary outcome</u>- 6MWT will be used to measure CRF during which individuals will be asked to walk continuously for six minutes on a flat, indoor surface around cones (separated by 100ft).</p> <p><u>Secondary outcomes- Psychological</u>- UCLA Loneliness Scale will be used to assess subjective feelings of loneliness. The PANSS will be utilized to assess psychiatric symptoms.</p> <p><u>Secondary outcomes- Biological</u>- We will measure weight, BMI, and waist circumference at all assessments. We will examine these characteristics to determine if they changed as a result of increasing exercise. Resting Systolic/Diastolic Blood Pressure and RHR will also be assessed following standardized procedures.</p>
Safety Evaluations	<p>A safety plan for the walking groups will be developed prior to the initiation of the study with Drs. Battaglini and Jarskog, as well as the study clinicians.</p>
Statistical And Analytic Plan	<p>Analyses will primarily be descriptive in nature. We will calculate means, standard deviations, and within-group effect sizes of the primary outcome (CRF) and secondary outcomes (loneliness, symptoms, weight, BMI, waist circumference, resting heart rate, and blood pressure). Additionally, we will examine means, standard deviations, and within-group effect sizes of intermediate targets (self-determination basic needs and autonomous motivation) and proximal outcomes (minutes spent walking and daily steps).</p>
DATA AND SAFETY MONITORING PLAN	<p>Dr. Jarskog will function as the Project Medical Officer. An independent physician will serve as the Medical Monitor (Dr. Karen Graham, from the Department of Psychiatry).</p>

1 BACKGROUND AND RATIONALE

Individuals with schizophrenia spectrum disorders (SSDs) have a life expectancy up to 25 years shorter than individuals in the general population primarily due to elevated levels of chronic physical and medical illnesses (1-4). Premature mortality in this population may be explained by high levels of six known modifiable risk factors for mortality: high blood pressure, smoking, raised glucose, physical inactivity, obesity, and high cholesterol (5-7), with physical inactivity and smoking being the strongest contributors to this risk (8, 9). Specifically, cardiorespiratory fitness (CRF) impacts not only cardiovascular mortality but also all-cause mortality (10-13), including in individuals with SSDs. Thus, physical inactivity contributes to significantly elevated rates of chronic medical diseases, especially cardiovascular disease (CVD) in individuals with SSDs (1, 5, 6, 14, 15). Further, despite reductions in mortality from CVD in the general population over the past 20 years, rates in people with SSDs have remained high (16, 17). Indeed, sedentary behavior and poor CRF among individuals with SSDs relative to the general population (13, 18-21) are likely major contributors to the premature mortality in this at-risk population. As a result, the potential benefits of interventions that increase physical activity (PA) in this population are substantial and could have a meaningful impact on public health.

Studies examining the effects of exercise on physical and mental health in individuals with SSDs have yielded encouraging results (22-24). Indeed, well-designed multi-component interventions that target exercise and diet, such as the ACHIEVE trial and the In SHAPE program, led to weight-loss and improved fitness in individuals with serious mental illness (25-27). However, these findings are tempered by questions of long-term accessibility and sustainability. Specifically, the In SHAPE program involved individual meetings with a trainer and continued access to a gym, perks that are inaccessible to most individuals with SSDs after study completion (26, 28-33). While a strength of the ACHIEVE trial was housing it in psychiatric rehabilitation settings, not all people with SSDs have access to such programs. In addition, attendance at the intervention sessions waned after the first 6 months of the study, which the authors attributed to hospitalizations and social issues (19) (p. 1601); however, decreasing subject motivation may have also played a role.

Prior work has been largely unsuccessful in overcoming the many barriers faced by individuals with SSDs. Specifically, exercise participation is hampered by lack of access and cost (e.g. personal trainers), biological factors such as physical health problems, social variables such as loneliness and limited social support, and self-regulatory problems (e.g., forgetting to exercise, being overwhelmed) (34-43). And, most interventions fail to address motivation, a critical factor for initiating and sustaining exercise, particularly for people with SSDs (44). Ironically, even work that has directly targeted motivation in this population (45) observed difficulties in promoting long-term adoption and sustained exercise after the program ends (46). These findings speak to the need for additional strategies to sustain motivation and ensure the effective translation of motivation into action. Thus, interventions aimed at this population should be designed and delivered in ways that address the substantial barriers to exercise, so as to promote the adoption and long-term maintenance of physical activity (47, 48).

Given the importance of motivation and translating intentions to actions, our treatment model is rooted in both self-determination theory (SDT) (49, 50) and implementation intentions (i.e., if-then plans) (51). SDT is a prominent theory of motivation which is highly suited for exercise interventions (52). SDT posits that the fulfillment of three basic psychological needs: autonomy, relatedness, and competence facilitates autonomous motivation (i.e. motivation due to one's own choice rather than as a result of external factors) (50). Autonomous motivation, in turn, is associated with levels of exercise participation in the general population (52, 53) and in people with SSDs (54).

If-then plans have the structure if (opportunity/obstacle)-then I will (response) and engender associations that mimic the effects of habits (55). If-then plans create mental links between good opportunities to act and responses that move the person towards their exercise goal (e.g., “If I have to go shopping for 1-2 items, then I will walk rather than drive to the store!”) or between obstacles to exercise and responses that will be effective in overcoming those obstacles (e.g., “If I am tempted not to exercise, then I remind myself how proud I feel at the end of the session!”). Two separate meta-analyses revealed that if-then plans were highly effective in increasing physical activity [ES = .31 and .38] (56, 57) and led to sustained behavior change one year (58-61) and two years (62, 63) post-treatment. If-then plans have also demonstrated effectiveness among samples with psychiatric and clinical diagnoses (64) including people with SSDs (65). Importantly, autonomous motivation and if-then plans are known to combine synergistically, and engender better outcomes compared to the use of either strategy on its own (66, 67).

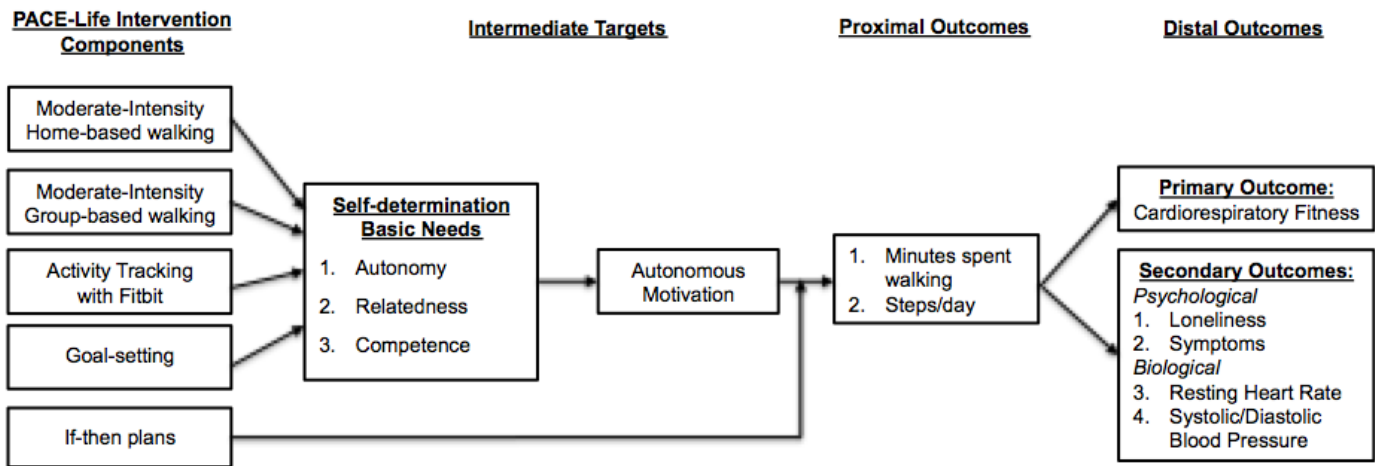
In addition to considering motivation and intention translation, we also sought to develop an exercise intervention that involves minimal staff resources, that is free and easy to access, and has the potential for long-term sustainability. Thus, we chose an intervention that requires no equipment or special training, and can be done anywhere: Walking (68, 69). Research has shown that walking leads to improved physical health, well-being, and weight loss (70-73). Furthermore, walking without dietary change has been shown to improve CRF (10, 74, 75), and reduce the risk of all-cause mortality (76), premature death (77), and the rate of cardiovascular disease (78) in the general population. Dose-response analyses have determined that the strongest health benefit accrues within the first 120 minutes per week of walking, further highlighting the potential impact of increasing PA among sedentary individuals (76). Moreover, given the widely accepted PA recommendations set forth by the American College of Sports Medicine (ACSM) (79) and by the International Organization of Physical Therapy in Mental Health (IOPTMH) (42), walking at a moderate-intensity level should be prioritized (See section C.3. for more details).

A valuable way to facilitate the initial engagement of exercise and address the barriers of social isolation in individuals with SSDs is through group-based interventions, as they promote social interaction, camaraderie, and social support (36-39, 80). Group-based interventions also impact motivation by offering the opportunity to develop friendships centered around a common goal, thus satisfying relatedness and competence needs and promoting self-efficacy (35). Walking programs in the general population that promote social support also led to greater maintenance of behavior change (81, 82). Therefore, social support (and reduction of loneliness) may play a critical role in helping individuals with SSDs initiate and adhere to exercise programs (35).

A critical component of goal setting and attainment is being able to monitor progress, which can be achieved via physical activity tracking devices. Pedometer use leads to an increase in PA – they are considered acceptable and are highly useful for setting PA goals (83-85), which helps to facilitate changes in exercise behavior (86). In fact, pedometers are the most cost-effective means of increasing PA in the general population (87). In a systematic review of 26 studies, pedometer use resulted in significant increases in PA (26.9% over baseline) (70). With recent advances in sensor and Bluetooth technologies, new physical activity monitors have emerged and are currently commercially available (e.g., Fitbit), which also allow the measuring of walking intensity (e.g., through heart rate; See Section C.3.).

Figure 1

Proposed Model



The model above illustrates how our proposed intervention, PACE-Life) will lead to increased exercise and improved outcomes. Specifically, PACE-Life includes five primary components: home-based walking, group-based walking, activity tracking, goal-setting, and if-then plans, four of which impact the SDT basic needs and one of which enhances autonomous motivation. Specifically, homebased walking targets autonomy needs (as individuals can do this independently), group-based walking targets relatedness needs, and activity tracking and goal setting target competence needs. Satisfaction of each of the SDT needs leads to the intermediate target of increased autonomous motivation. PACE-Life subjects also form if-then plans which serve to enhance the impact of autonomous motivation (66, 67) and promote actual exercise behavior (56, 57). Engaging these intermediate targets in turn engenders the proximal outcomes of greater exercise participation (as measured by minutes spent walking per week and steps/day). Finally, increased exercise should lead to the improved primary outcome of CRF as well as improved secondary outcomes of loneliness, symptoms, resting heart rate, and systolic/diastolic blood pressure.

The proposed research is highly innovative in at least three respects. First, the simplicity and practicality of PACE-life is a key innovation. As noted above, most previous interventions for individuals with SSDs required gym equipment (e.g., treadmills) as well as professional supervision to engage in exercise, thus limiting both sustainability and scalability (22-24, 26). The field demands pragmatic interventions that are low in resource costs and can be rapidly translated into clinical practice (48, 88). Our walking intervention is both cost-effective and highly accessible given that the group-based portion will be implemented in the vicinity of the outpatient clinic and the home-based portion will be completed at locations selected by subjects (e.g., outdoors on residential streets or indoors at malls during inclement weather).

Second, the focus on cardiorespiratory fitness (CRF) is novel. Although CRF has long been identified as a significant predictor of health, it has only recently received attention in exercise intervention research among individuals with SSDs. A meta-analysis on the effects of exercise on CRF in individuals with SSDs (12) revealed only 3 published randomized controlled trials that examined this health indicator (32, 89, 90). Vancampfort and colleagues (13) concluded that despite the few available studies on CRF in schizophrenia, improvements in this domain are possible and may provide a “novel and valid exercise target that could lead to reductions in premature mortality in people with schizophrenia” (p. 456). In addition, we will measure CRF

Therefore, our intervention will include both clinic-based sessions and instructions for home-based sessions to prioritize feasibility and sustainability.

Rationale for moderate-intensity walking as exercise modality. Walking is the primary form of exercise in PACE-life given its accessibility and association with meaningful fitness and health outcomes. PACE-life will combine walking groups and Fitbit with heart rate monitoring to encourage moderate-intensity walking in individuals with SSDs. The goal of PACE-life is to facilitate engagement in 150 min/week of moderate-intensity walking spread throughout the week, which is consistent with recommended fitness guidelines set forth by the ACSM (79) and by the IOPTMH (42). To achieve this goal, we will employ a stepwise approach of exercise participation to provide individual tailoring and reduce the likelihood of dropouts (103). Specific details and rationale of this approach are discussed below:

Overview and rationale of stepwise approach. Stepwise approaches to exercise participation are often recommended for use with sedentary populations to reduce the risk of injury and dropouts (32, 103). Typically, these interventions will begin at low intensity and low frequency, and as individuals become more physically active, the intensity and frequency increase. This strategy is especially relevant to individuals with SSDs as they are quite sedentary and have little experience with consistent participation in exercise. Furthermore, individuals need to engage in moderate-intensity exercise, defined as exercising within 60-70% of heart rate reserve (HRR), in order to achieve meaningful changes in CRF (103). In sedentary individuals, moderate to high intensity exercise may not be achievable immediately in the first weeks of the program and starting physically deconditioned individuals in a program that is too intense can be physically dangerous and lead to significant dropouts (103, 106). As a result, a step-wise approach that begins at a lower-intensity and increases to moderate intensity is more appropriate and has been successfully implemented in SSDs (32, 89). For the present study, low and moderate intensity exercise will be operationalized by HRR (103, 106) where Low-intensity Exercise = 50-60% of HRR and Moderate-intensity exercise = 60-70% of HRR.

We (Battaglini, PI) demonstrated the potential benefits of a step-wise exercise program in African-American breast cancer survivors that began at a low intensity and later progressed to moderate intensity (107). The results showed a high completion rate (76%) and adherence to walking goals (70%).

2.2 SUBJECTS

Based on the grave health concerns, physical inactivity, and growing urgent calls for action in individuals with psychotic disorders (116, 117), 14 study subjects will be recruited from the UNC Schizophrenia Treatment and Evaluation Program (STEP) clinic in Raleigh, North Carolina. All subjects will have a primary diagnosis of a schizophrenia spectrum disorder. To obtain an estimate of IQ and to rule out any individuals with possible mental retardation, we will administer the WASI, which is comprised of Matrix Reasoning, Vocabulary, Similarities, and the Block Design subtests. Additional demographic and clinical information that will be collected as self-report for possible use as covariates includes: 1) demographics: age, sex, ancestry, education, parent education; 2) health: smoking, substance use, current medications, duration of outpatient treatment, diet, physical activity, height, weight, BMI, and waist and hip circumference.

2.2.1 INCLUSION CRITERIA

1. DSM-V diagnosis of a Schizophrenia Spectrum Disorder (Schizophrenia, Schizoaffective Disorder, Brief Psychotic Disorder, Schizophreniform Disorder, and Unspecified Schizophrenia Spectrum and Other Psychotic Disorder)
2. Age 18 or above, both genders, and any ancestry

3. IQ>70
4. No hospitalizations in the last 3 months
5. Clinically stable (no medication changes within the past month)
6. Are not already engaging in consistent moderate-intensity exercise (cutoff = 60 min/week for the past 6 months)
7. Present with no contra-indication to engage in regular moderate intensity exercise based on the ACSM guidelines (118). If individuals answer yes to one or more items on the of the PAR-Q, a questionnaire that assesses cardiovascular risk factors, she/he will require further evaluation by a physician prior to participating in the study
8. Willing and able to provide informed consent.

2.2.2 EXCLUSION CRITERIA

1. Pregnant women will be excluded because pregnancy alters autonomic and immune responsiveness, increase weight gain, and can influence heart rate.

3 ASSESSMENT OF DATA

At this stage of treatment development, specific outcomes include:

1. Feasibility (Can PACE-life be delivered within this treatment setting?)
 - Will determine if recruitment procedures yield the target number of subjects in 3 months
 - Will determine feasibility of assessments based on subject compliance rates
2. Tolerability (How well is PACE-life accepted by the subjects?)
 - Will be evaluated by examining subject attendance to groups, adherence to homebased component of program, Fitbit usage, and dropout rates.
3. Intervention adherence
4. Evaluation of PACE-life. We will evaluate feasibility in two ways. First, we will determine if recruitment procedures yield the target number of subjects in 3 months. Second, we will determine feasibility of assessments based on subject compliance rates. The tolerability of PACE-life will be evaluated by examining subject attendance to groups, adherence to homebased component of program, Fitbit usage, and dropout rates.

3.1 OUTCOMES

The central hypothesis is that an intervention that increases physical activity as measured by minutes spent walking (at the prescribed intensity) and steps/day will result in improved health and lowered risk for premature mortality as evidenced by superior CRF (primary outcome), and on a variety of secondary outcomes (e.g. blood pressure). Guided by strong preliminary data and grounded in SDT, this hypothesis will be tested via three specific aims:

1. To develop a manual-based walking intervention for individuals with SSDs: PACE-Life. The manual will include guidelines for goal setting and translating intentions into behaviors (i.e., “if-then” plans), instructions for the group-based walking activity and home-based walking activity (which includes Fitbits), and increasing exercise intensity in a step-wise manner.
2. To examine the feasibility of implementing PACE-life at a community mental health clinic in an open trial of 14 individuals with SSDs.

3. We will also examine the impact of PACE-life on intermediate targets (autonomous motivation and SDT needs), proximal outcomes (minutes spent walking and steps/day), the primary outcome of CRF, and secondary outcomes.

We hypothesize that PACE-life will be associated with:

- Improved proximal and primary outcomes including greater minutes/week spent walking and steps/day and increased CRF at mid-treatment (3 months), post-test (6 months), and one-month follow-up;
- Decreases in secondary outcomes including loneliness, SSD symptoms, resting heart rate, and blood pressure at mid-point, post-test, and one-month follow-up.
- Higher levels of theoretically-relevant, intermediate targets (autonomous motivation and SDT needs) at mid-treatment, post-test, and one-month follow-up.

4 STUDY DESIGN

During this phase of the trial, 14 subjects will be assigned to one of two walking groups of 7 subjects each. The exercise intervention, PACE-Life, will last for 24 weeks and includes both group walks and independent walks (done at a location of the subject's choosing). Subjects will be asked to complete a total of 5 in-person assessments at screening, baseline, mid-point, post-test, and 1-month follow-up.

4.1 INTERVENTION

Groups will occur twice per week for 30 minutes for the entire intervention without changes in frequency and duration. The intensity, however, of both group walks and home-based walks will increase throughout this intervention in a stepwise fashion to create an exercise dose response to maximize impact on CRF. The rationale for this plan hinges on both the importance of maintaining cohesion and social interaction as well as the practicality concerns regarding sustainability. Furthermore, we tested a 2x/week group schedule in the pilot with high attendance rates and feedback (overall attendance: 84%). The intervention overviews are given below:

Weeks	# of Clinic-based Group Sessions	Duration of Group Sessions	# of Home-based Sessions	Duration of Home-based Sessions	Intensity
1-3	2	30 Minutes	0	30 Minutes	50-60% of HRR
4-6	2	30 Minutes	0	30 Minutes	50-65% of HRR
7-9	2	30 Minutes	1	30 Minutes	60-65% of HRR
10-12	2	30 Minutes	1	30 Minutes	65-70% of HRR
13-15	2	30 Minutes	2	30 Minutes	65-70% of HRR
16-18	2	30 Minutes	2	30 Minutes	65-70% of HRR
19-21	2	30 Minutes	3	30 Minutes	70% of HRR
22-24	2	30 Minutes	3	30 Minutes	70% of HRR

PACE-life will be integrated into the STEP outpatient clinics in Raleigh, NC and Carrboro, NC. The group walks will occur in the surrounding area around the clinics on sidewalks, bike trails, and residential streets. Goal setting groups and all assessments will take place in a conference room at the clinic.

4.1.1 GOAL-SETTING

Goal-setting will include setting goals for the upcoming week in terms of number of steps as well as how many intensity walks (at specified heart rate) that individuals plan to complete. Goal-setting materials draw upon SMART (specific, measurable, achievable, relevant, and time-based) principles as well as implementation intentions (i.e., if-then plans) and mental contrasting. Specifically, subjects will be asked to imagine what the best thing would be about walking/exercise more and then identify the biggest barriers. They will then be encouraged to create if-then plans about how to manage barriers to exercising more. This procedure has been extensively examined in social psychology research and has been shown to be successful in helping individuals increase their exercise (93). Goal-setting groups will be audiotaped and subsequently coded for fidelity to the protocol.

4.1.2 FITBITS

All subjects will be provided with a Fitbit that is labeled with a subject number. All Fitbits are paired to a Fitbit account with the username (pacelifeIDnumber@gmail.com) and password (pacelife). Data from Fitbit devices can be synced to the corresponding account and accessed through Fitbit.com. Subjects will be provided information about their accounts should they want to look at the data but will be asked not to change any of the settings as we will be using data for tracking steps/day and minutes spent walking. No identifying information will be inputted in the Fitbit.com account for subjects.

4.2 STUDY PROCEDURES AND MEASUREMENTS

4.2.1 SCREENING VISIT

The following measures will be examined at screening:

- Demographics- We will collect information on age, sex, ancestry, education, parent education, smoking, substance use, current medications, duration of outpatient treatment, and diet.
- Intelligence- In adherence with our inclusion criteria that subjects must have an IQ greater than 70, the Wechsler Abbreviated Scale of Intelligence (WASI) will be administered.
- Medical History- A licensed physician will complete the Medical History and Physical Exam Form. They will also complete a 10 minute physical to ensure health.
- Current Physical Activity- In order to ensure that subjects are healthy enough to begin the walking program, subjects will complete the Physical Activity Readiness Questionnaire (PAR-Q).
- Diagnosis-The Structured Clinical Interview for the DSM-V (SCID) will be utilized to assess symptoms. The SCID is a semi-structured interview that assesses for DSM diagnoses. The SCID will be used to verify that subjects have a schizophrenia spectrum diagnosis before they are enrolled in the study. Raters will be trained to conduct the SCID to a gold standard of reliability (i.e., intraclass correlation > .80).

4.2.2 BASELINE, MID-POINT, POST-TEST, 1 MONTH FOLLOW-UP

The following measures will be examined at the baseline, mid-point, post-test, and 1 month follow-up study visits:

- Demographics- We will collect information on age, sex, ancestry, education, parent education, smoking, substance use, current medications, duration of outpatient treatment, and diet.

- Minutes Spent Walking- We will utilize data recorded from Fitbits to assess minutes spent walking (by syncing Fitbits to corresponding Fitbit.com accounts and loading deidentified data onto study laptops).
- The Short Form International Physical Activity Questionnaire (IPAQ), a valid self-report measure, to assess changes in physical activity. The IPAQ Short Form is a four-item scale that assesses frequency and duration of walking, moderate-intensity exercise, vigorous-activity exercise, and sitting.
- Steps/day. We will also collect daily step numbers using Fitbit data downloaded onto study laptops from Fitbit.com at group sessions.
- Cardiorespiratory fitness (CRF)- CRF will be measured using the 6-minute walk test (6MWT) during which individuals are asked to walk continuously for six minutes on a flat, indoor surface around cones (separated by 100ft) and the primary outcome is the total distance walked. The 6MWT is recommended for use with sedentary individuals and to evaluate the impact of an exercise intervention. Moreover, the 6MWT has been successfully administered to individuals with SSDs, including those in our pilot trial. As a result, we plan to utilize the 6MWT as our primary measure of CRF.
- Self-determination Basic Needs. The self-determination basic needs of autonomy, relatedness, and competence will be measured with two scales. The Basic Psychological Need Scale-in General is a self-report measure that assesses general satisfaction with autonomy, relatedness, and competence. Three subscale scores are produced. The Basic Psychological Needs in Exercise Scale (BPNES) is self-report scale that measures the extent to which basic needs are satisfied through exercise.
- Symptoms- the Positive and Negative Syndrome Scale (PANSS) will be utilized to assess symptoms specifically present in schizophrenia spectrum disorders. The PANSS is a semi-structured interview assessing positive symptoms, negative symptoms, and general psychopathology symptoms. Raters will be trained to conduct the PANSS to a gold standard of reliability (i.e., intraclass correlation > .80)
- Resting Systolic/Diastolic Blood Pressure and RHR will be assessed following standardized procedures at the STEP clinic. Individuals with SSDs will be placed in a sitting position in a quiet room, with lights dimmed, and will be asked to remain quiet and relaxed with their eyes closed while avoiding movement for approximately 10 minutes. After 10 minutes, research team members will assess their RHR via palpation for 1 minute. Following the assessment of RHR, resting BP will be assessed using an automated blood pressure device following the manufacture standard procedures. Given the high rates of hypertension in this population, the assessments of blood pressure changes throughout this exercise intervention are significant indicators of potential benefits of exercise on improvements in physical health. Further, given the sedentary lifestyle of many individuals with SSD, changes in RHR upon the initiation of exercise is a valuable indicator of fitness and physical health.
- Autonomous Motivation- Given the available research indicating that autonomous motivation is related to negative symptoms and subsequent engagement, maintenance, and adoption of exercise in individuals with SSDs, we will measure this construct with The Behavioral Regulation in Exercise Questionnaire-2 (BREQ-2).

- **Enjoyment of Walking-** Given that enjoyment of the walking program can impact adherence to the treatment, we will measure this construct with the Physical Activity Enjoyment Scale (PACES).
- **Planned Behavior-** Available research has shown that intentions, self-efficacy, attitudes and norms are correlated to adherence in exercise. All items are derived from established measures of theory of planned behavior variables (e.g., Conner & Sparks, 2015). Responses are all on 7-point scales. The order of items would be randomized.
- **Loneliness:** The UCLA Loneliness Scale is a brief self-report measure that will be used to assess this construct.
- **Weight, BMI, and Waist/hip Circumference-** We will measure weight, BMI, and waist/hip circumference at all assessments using the scale and measuring tape located at the STEP clinic.
- **Exit Survey on PACE-life-** At the conclusion of the open trial, we will administer a brief questionnaire to the subjects regarding satisfaction and acceptability that will have both forced choice and open-ended questions.

5 STATISTICAL ANALYSES

5.1 DATA ANALYTIC PLAN

Feasibility will be defined by our ability to meet our recruitment targets (14 people), frequency of engagement in the intervention by participants (group attendance and activity tracking/home-based adherence), and feedback on the intervention from participants. Feedback from participants will be incorporated into modifying the manual for the RCT.

Analyses of intermediate and primary outcomes will primarily be descriptive in nature. We will calculate means, standard deviations, and within-group effect sizes of intermediate targets (SDT needs and autonomous motivation), proximal outcomes, including minutes spent walking, and steps/day, the primary outcome of CRF, and the secondary outcomes including RHR, blood pressure, loneliness, and symptoms. Further, we will calculate the percentage of the sample meeting the threshold for clinically significant changes in our outcomes of 6MWT, steps/day, and minutes spent walking to determine whether these changes are clinically meaningful. Finally, we will explore the relationship between baseline IQ, treatment adherence and outcome improvement so as to determine if cognitive functioning is associated with treatment response.

5.2 POWER ANALYSIS

As this is an open trial, we will not conduct a power analysis for the participant size of the study. We are expecting to recruit 14 participants for this study based on the successful recruitment of the previous pilot trial, which recruited 16 total (IRB # 16-2057).

5.3 DATA MANAGEMENT

All data will be entered by trained research assistants using Qualtrics software. Double data entry will be required for information not directly entered by the participants. Double data entry will also be entered by trained research assistants using Qualtrics software. All data analysis will be conducted by statistician, Oscar Gonzalez.

6 RISKS AND BENEFITS

There are some risks associated with the proposed research. First, collection of the clinical information may be associated with anxiety or embarrassment due to revealing personal information. Second, there is the risk that confidential personal information could be disclosed to others outside of the research staff. Third, there is risk in participating in the 6-minute walk test as a measure of cardiorespiratory fitness (CRF). Finally, there is risk associated with participating in the walking groups, such as ankle, leg, and back injuries, and cardiovascular distress.

6.1 Monitoring Risks

To address subject anxiety or embarrassment due to revealing person information, we have trained research staff who are experienced in working with individuals with schizophrenia spectrum disorders. They have been trained to put subjects at ease, let them take their time, and to conduct interviews in private rooms.

To address the issue of accidental disclosure of personal information to others outside of the research staff, we will obtain a NIH Certificate of Confidentiality for the study. In addition, identifying research subjects by study number on all research documents minimizes the risk of breach of confidentiality. Study documents that must contain personal information, including the informed consent document, and the document that links study ID number to personal identifying information (necessary due to the longitudinal nature of the open trial and RCT) are kept in locked filing cabinets in locked rooms. Research data will be kept on password-protected drives, and our computer systems are HIPAA compliant. All study staff participate in annual human subject training that includes education about responsibilities to minimize risk that confidentiality may be breached.

To address the potential health risk associated with participation in the walking groups as well as the 6-minute-walk-test, all subjects will have a medical history and physical examination performed by Dr. Jarskog as part of the Screening procedures. Dr. Jarskog will also administer the PAR-Q, a widely used questionnaire to assess cardiovascular risk factors in advance of exercise initiation. For any subject who answers “yes” to one or more items on the PAR-Q, Dr. Jarskog will contact their PCP to discuss appropriateness for the subject to participate and help facilitate further evaluation as needed. In addition, the research staff will be trained by one of the PIs, Claudio Battaglini, an exercise physiologist, on the 6-minute-walk-test procedure. Further, if an individual shows any distress during this assessment, she or he will be instructed to stop the assessment and the research staff will contact Dr. Battaglini and Dr. Jarskog.

To address the issue of physical injury or cardiovascular distress during the walking groups, the study clinicians will be trained by Dr. Battaglini on potential cardiovascular warning signs, and appropriate responses to any reported symptoms. Further, a safety plan for the walking groups will be developed prior to the initiation of the study with Drs. Battaglini and Jarskog, as well as the study clinicians. The walking groups will be conducted on level terrain, to minimize any potential leg, ankle or back injuries. Finally, it should be emphasized that this project is testing the impact of moderate-intensity walking, a less physically demanding and inherently safer activity when compared to other more rigorous activities that could pose greater cardiovascular and joint-related risks.

Should any subject experience any problems during the study, our research team has trained staff that will be able to provide immediate care on-site. Subjects will be referred for additional care to the appropriate providers on campus, such as Campus Health Services or the UNC Hospitals Emergency Department, if necessary.

6.2 NON-SIGNIFICANT RISK DOCUMENTATION

Pregnant women will be excluded because pregnancy alters autonomic and immune responsiveness, increase weight gain, and can influence heart rate.

6.3 POTENTIAL BENEFITS OF THE RESEARCH TO SUBJECTS AND OTHERS

The subjects who participate in the walking groups (in the open trial and RCT) may have a significant benefit on their cardiorespiratory fitness, which could have a subsequent impact on their overall physical and mental health. This study will provide currently unavailable information about the potential feasibility and effectiveness of a scalable and accessible exercise intervention for individuals with schizophrenia spectrum disorders. The risks of the study are minimal and reasonable in light of the knowledge gained.

6.4 CONFIDENTIALITY OF DATA

Risks regarding confidentiality will be minimized by using code numbers instead of names on study data. The code and the data will be stored in separate locked files at Davie or Howell Hall on UNC's campus. Similar subject records are scrutinized regularly and our procedure will add an extra level of protection because the research case numbers will be different from subject numbers (random numbers not associated with date of birth) and the code will be unavailable to anyone outside of the research team. Audio recordings of weekly group sessions will be saved on our secure lab server and on OneDrive so that offsite investigators may review and provide feedback to the clinicians conducting the sessions.

Identifiable data will only be shared with the clinicians of subjects in the study with the permission of the subjects (obtained during informed consent). Clinicians will be contacted if issues arise related to safety during the trial. As part of the informed consent process, all subjects will provide the name and contact info of a clinician that we may contact if we become concerned about their safety (e.g., physical and/or mental health) during the course of the trial. We will not be sharing any confidential information with anybody outside of these clinicians.

Identifiable data will be maintained for 5 years following study completion. At that point, hard copies of identifiable data including consent forms and contact information will be shredded. Electronic data will be de-identified upon entry, with the exception of the subjects' birth dates for the purposes of calculating their exact age.

7 DATA SAFETY AND MONITORING PLAN

7.1 ADVERSE EVENTS

Dr. Jarskog (Co-I) will function as the Project Medical Officer and will be available on pager and cell phone to all co-investigators to discuss any safety issue that emerges over the course of the study. All adverse events (AEs) occurring during the course of the study will be documented and reported to Dr. Jarskog. All Serious Adverse Events (SAEs) will also be reported to the IRB and NIMH. The occurrence of AEs will be assessed during the study and the investigators will follow all AEs to the point of satisfactory resolution. An independent physician will serve as Medical Monitor (Dr. Karen Graham, from the Department of Psychiatry). AEs will be tracked over the course of the study and will be reported at the midpoint and endpoint of each walking group cohort to the DSC. All SAEs will be reported to the DSC within 24 hours of learning of the event.

7.2 SERIOUS ADVERSE EVENTS

AEs will be assessed to determine if they meet criteria for a SAE. SAEs, as defined by the FDA, will be systematically evaluated at each clinic visit. Any SAE will be reported to the IRB and NIMH. The initial SAE report will be followed by submission of a completed SAE report to each institution. In the event that a subject either withdraws from the study or the investigator decides to discontinue a subject due to SAE, the subject will have appropriate follow-up and/or stabilization. Follow-up will continue until the problem requiring hospitalization has resolved or stabilized with no further change expected, is clearly unrelated to study procedures, or results in death. Outcome of SAEs will be periodically reported to NIMH. A summary of the SAEs that occurred during the previous year will be included in the annual progress report to NIMH.

The trial period is defined from the time that the informed consent document is signed until 30 days after the last study visit. All serious AE's occurring during the trial period (including death due to any cause) or within 30 days after the last study visit will be communicated within 1 day of the investigator becoming aware of the event to designated personnel, using the telephone or fax numbers provided in the Study Reference Manual. Any fatal or life-threatening AE's will be reported immediately, but no longer than 1 day from the time the investigator becomes aware of the event. A causality assessment will be provided for all SAEs. Critical follow-up information on SAEs will be provided as soon as it is available, but no longer than 1 day from the time the investigator became aware of the information. Other essential, but not critical, information may be reported within the following 5 days. An SAE, as defined by the FDA for use in clinical trials (<https://www.fda.gov/safety/medwatch/howtoreport/ucm053087.htm>), is an adverse event that satisfies any of the following criteria:

- Results in death.
- Is immediately life-threatening, including potentially life threatening suicidal behavior or suicidal behavior that results in hospitalization.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability or incapacity.
- Is a congenital abnormality or birth defect.
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above. Examples would include allergic bronchospasm that requires treatment in an emergency department, or a seizure that does not result in hospitalization.

The causality of SAEs (i.e., their degree of relatedness to study treatment) will be assessed by the investigators.

7.3 DEATH

All deaths occurring within the trial period or within 30 days after the last day that the study intervention is administered will be reported within 1 day of the investigator becoming aware of the event. If an autopsy has been performed, results of the autopsy will be obtained and forwarded along with any available toxicology reports.

7.4 PREGNANCY

Pregnancy is an exclusion criterion and women who can become pregnant should use adequate methods of birth control as outlined in the inclusion criteria. Should a pregnancy occur it must be reported in accordance with the procedures described below. Pregnancy in itself is not regarded as an AE unless there is a

suspicion that an intervention may have interfered with the effectiveness of a contraceptive medication. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the subject was discontinued from the study. The Adverse Events/Side Affects form will be used for this purpose. All reports of congenital abnormalities/birth defects are SAE's. Spontaneous miscarriages should also be reported and handled as SAE's. All other outcomes of pregnancy must be reported on the Adverse Events/Side Effects form.

8 RECRUITMENT STRATEGY

Subjects will be recruited from the UNC STEP clinic in Raleigh (Wake County), North Carolina. STEP provides services to approximately 435 clients annually; 76% at STEP meet criteria for schizophrenia spectrum disorders (SSD). Clients will be approached about the study in a manner similar to what would happen in the real world outside of a research study. Specifically, psychiatrists, clinicians, and nurses will provide information to clients during appointments, groups, and in the clinic waiting area of a potential new exercise group. If the client is interested, then the research assistant will be notified to get in contact with the interested client. IRB approved flyers will also be posted at STEP.

We will supplement recruitment at STEP Wake, as needed, with assistance from the North Carolina Psychiatric Research Center (NCPRC) and STEP-Chapel Hill. Jarskog (Co-I) is the research director of the NCPRC. The NCPRC is co-located with the STEP clinic in Raleigh and has dedicated staff and space dedicated to outpatient research. The NCPRC is an outpatient research facility that is integrated into the UNC STEP Clinic of Wake County. The mission of the NCPRC is to study the pathophysiology of and advance treatments for schizophrenia and related disorders. Research conducted at the NCPRC is currently funded by the NIMH, NIDDK, foundations that support mental health research, and selective collaborations with the pharmaceutical industry. The NCPRC fosters active collaborative research both within and across departments at UNC-Chapel Hill and with other academic institutions. It also serves as a core facility where other investigators at UNC-Chapel Hill can conduct mental health-related research. STEP-Chapel Hill has 944 active clients. Over 75% have a psychotic disorder and approximately 56% are female. Finally, we will recruit individuals who have agreed to be contacted about future studies while they were subjects in past research studies conducted by Penn (~300 individuals with SSDs).

9 CONSENT PROCESS

Research staff will obtain informed consent directly from each subject. Staff obtaining the consent will provide the subject with a written document explaining the testing procedures and risks, and will answer any questions. We have several procedures in place to ensure that prospective participants fully understand the procedures, risks, and protections of the study. First, the consent form is written in easy to understand language. Second, the researcher reads the form to and with the potential subject, and invites questions after each section of the form. Third, the researcher asks the subject a series of questions about the study, such as what they are to do if they no longer want to participate, or what they would do if they experience any stress during the protocol (this is to be used as comprehension check before signing).

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